HORMESIS: Its Biomedical Foundations and Therapeutic Implications

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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.
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.
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 vs. Chemotherapy Dose

- Enhanced Tumor Growth
- Therapeutic Range

Cell Anti-Proliferation
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

- Maximum response (averages 130-160% of control)
- Distance to NOAEL (averages 5-fold)
- NOAEL
- Hormetic Zone (averages 10- to 20-fold)
- Control

Increasing Dose
Dose Response

High-Risk Group

Normal
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;

• Cell Signaling Pathway Assessment: Use of 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.
Effect of PAF on the Production of cAMP in Antigen Challenged Guinea Pigs
Effects of a Corticosterone on Prolactin Production in MTT/SM Cells (from an estrogen-induced mammotrophic tumor)
Effects Genistein on the Incorporation of Tritiated Thymine in Caco-2BBe Cells

Genistein (µmol/L)

% Control

0.0 2.0 3.7 26.0 52.0 111.0
Effects of Nicotine on the Proliferation of Human Osteoblast-Like Cells, MG63, at 24 Hours (similar findings were reported at 48 and 72 hours)
Effects of Histamine on Progesterone Production by MA-10 Cells

**Histamine (M)**

- H2
- H1

% Control

- 0.00E+00
- 1.00E-10
- 1.00E-09
- 1.00E-08
- 1.00E-07
- 1.00E-06
- 1.00E-05

* Effects indicated by asterisks
Effects of Noradrenaline on Renin Release from Rat Juxtaglomerular Cells

Noradrenaline (M)

β-adrenergic

α-adrenergic

% Control

0.00E+00 1.00E-09 1.00E-08 1.00E-07 1.00E-06 1.00E-05 1.00E-04 1.00E-03
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
Effects of Acute Ethanol on Overall Social Activity of Adolescent Rats Tested on Postnatal Day 30
Number of Open Arm Entries in the Elevated Plus Maze in Male C57BL/6 Mice Treated with DHEA
Effect of Different Doses of Morphine on PTZ-induced Seizure Threshold

Morphine (mg/kg)
Methanol and Fruit Fly Longevity

- **Females**
- **Males**

Longevity (% control)

Methanol (％)
Effect of Sodium Arsenate on PHA-Treated Bovine Lymphocytes
The Effects of Methyl Mercury on Viability as Measured by Mitochondrial Dehydrogenase Activity in the D407 Cell Line
Cardio-protective Effects of Resveratrol in Experimental Studies

- Myocardial Infarct Damage
- Cardiomyocyte Apoptosis
Effects of Curcumin on the Extent of Wound Healing in Human Skin Fibroblasts ASF-2
Effects of Curcumin on Chymotrypsin-Like Proteasomal Activity of Human Keratinocytes

% Control

Curcumin (µM)
Gamma Rays and Mouse Lung Adenomas

Incidence (% control)

Gamma Ray Dose (rad)
Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation

Survival (%)

Age (Weeks)

Non-irradiated

0.65 mGy/hr

90 weeks

70%

40%
Appearance of db/db mice at 90th week of age
Effect of Gamma Rays on the Life Span of Female House Crickets

Days (% of control)

Gamma Rays (R)
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)
Effect of DDT on Liver Foci Formation in Male F344 Rats

GST-P Positive Foci (% control)

DDT (ppm)
Bladder Tumor Incidence Adjusted for Time in ED01 Megamouse Study

% Control

AAF (ppm)

0 30 35 45 60 75 100 150

0 20 40 60 80 100 120 140 160 180 200 220 240

*
HORMETIC APPLICATIONS

• DRUG DEVELOPMENT
  – Anxiolytic agents
  – Anti-seizure drugs
  – Memory enhancement
  – Osteoporosis drugs
  – Wound healing preparations
KEY OBSERVATIONS

• Pre- and post-conditioning display the hormetric 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 of 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/biofilms;
KEY OBSERVATIONS

• Harmful Applications
  – 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.
CONCLUSIONS

• Hormesis can play a significant role in drug discovery, development, and evaluation.

• Hormesis should become incorporated into educational programs dealing with the dose response.
CONCLUSIONS

• Hormesis has the potential to significantly impact both clinical medicine and the public health.