

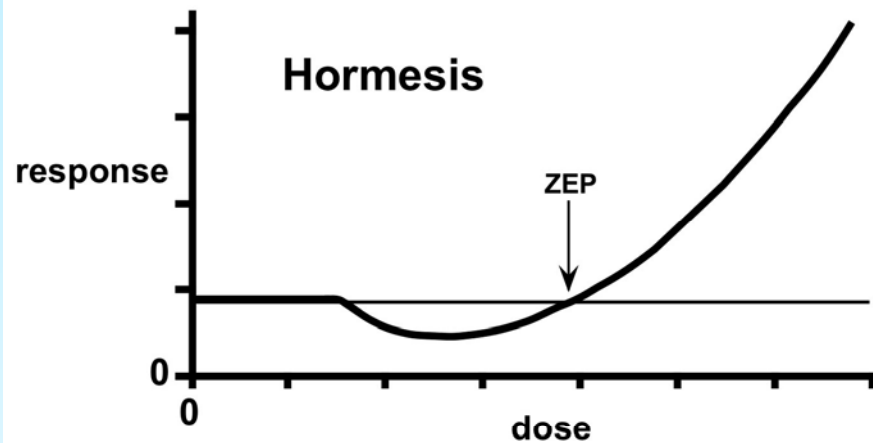
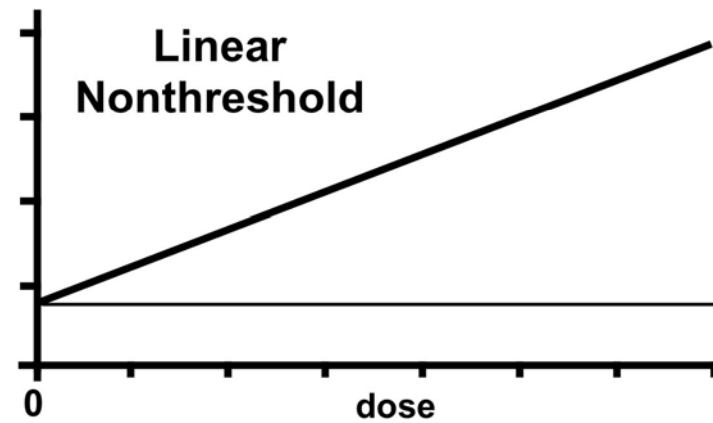
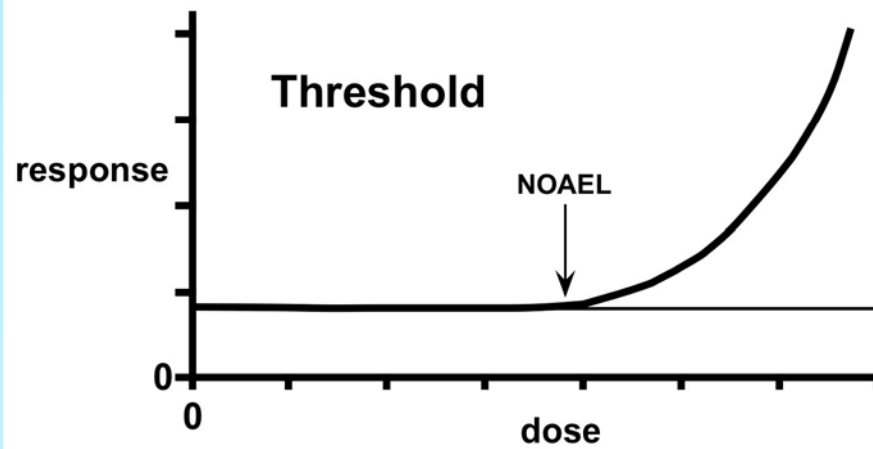
A Perspective on the Scientific, Philosophical & Policy Dimensions of Hormesis

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Dose-Response Models in Toxicology



Adapted from
G.R. Hoffmann and W.E. Stempsey,
BELLE Newsletter 14(3): 11-17, 2008.

Dose-Response Models

Three principal dose-response models:

- Threshold.**
- Linear nonthreshold (LNT).**
- Hormesis.**

**Threshold model & the related sigmoid curve:
the standard in toxicology.**

**LNT model: prevailing model for mutagenesis &
carcinogenesis.**

**Hormesis: a challenge to the threshold & LNT
models based on biphasic dose responses.**

"The intolerance of New Englanders is overwhelming. There is never a curve -- all the lines are hard and straight."

Gertrude Stein

Radcliffe College, 1897

Definitions of Hormesis

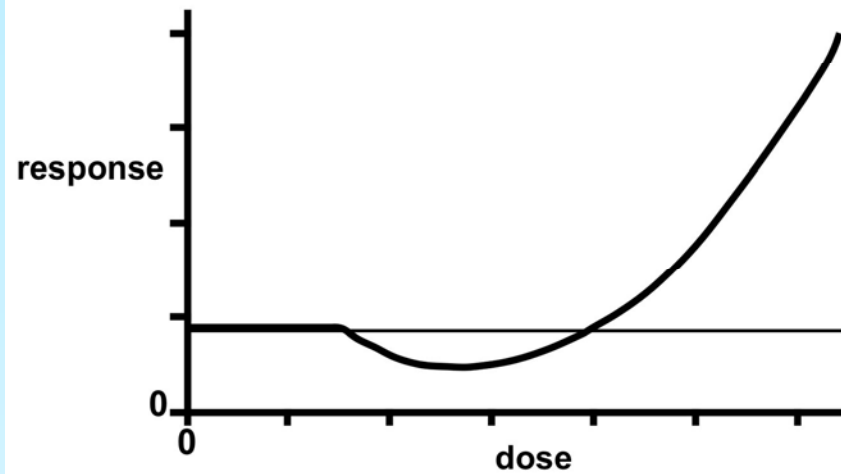
Opposite effects at high & low doses.

U- or J-shaped curves.

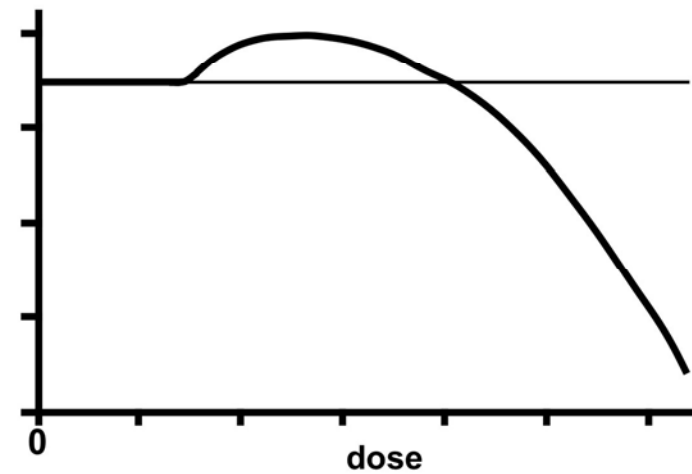
A broad network of biological stress responses.

Hormesis Dose-Response Model

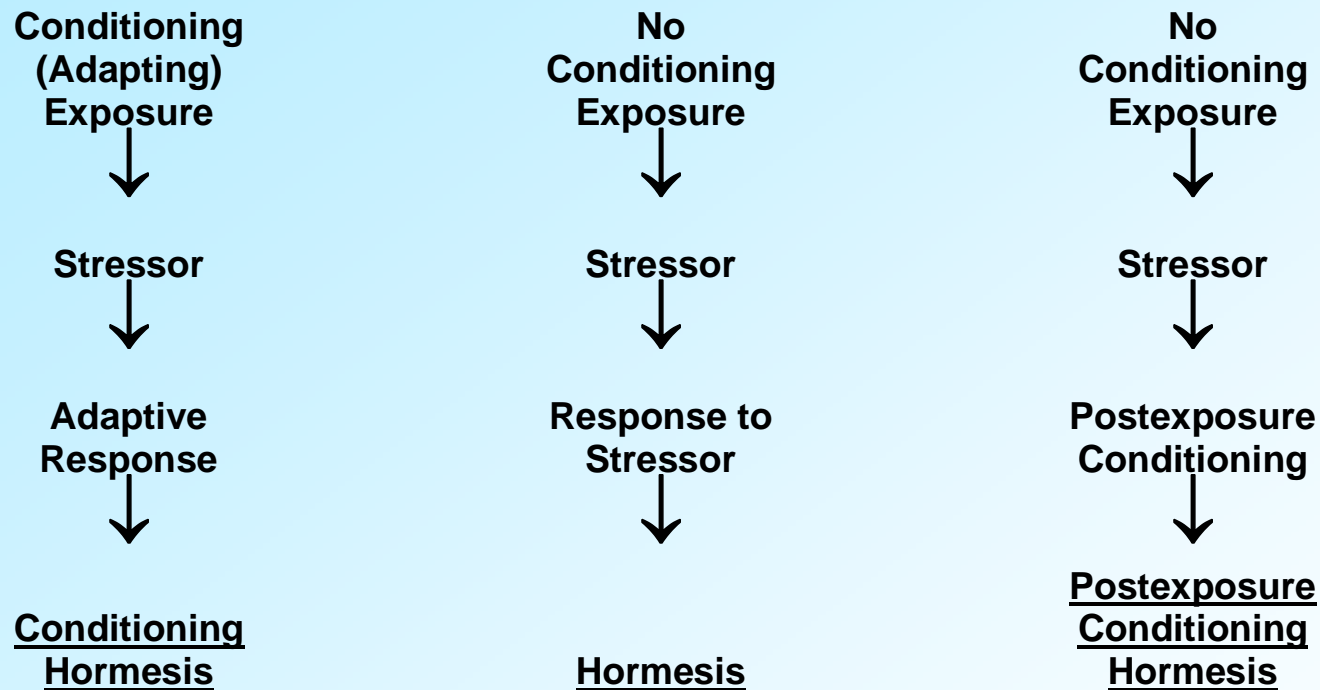
"J-shaped curve"



"inverted-U curve"



Biological Stress-Response Terminology



Examples:

Physiological, Radiation, or Chemical Conditioning Hormesis.

Physiological, Radiation, or Chemical Hormesis.

Physiological, Radiation, or Chemical Postexposure Conditioning Hormesis.

Adapted from E.J. Calabrese et al.

Toxicology & Applied Pharmacology 222:122-128, 2007

Points of Contention

Default models for low doses.

Relationship to benefit & harm.

Evidence for Hormesis

There is strong evidence that hormesis is real.

Hormesis is prevalent in surveys of toxicology literature.

Analysis of databases from systematic chemical testing supports the hormesis model.

Quantitative characteristics of the hormetic response give it conceptual coherence.

Yeast Growth at Nontoxic Doses

(percentage of control growth; values > 100% suggest hormesis)

Strain	Dosage Range of the Highest Nontoxic Dose [†]			
	3.7-11 μ M (high toxicity)	11-33 μ M	33-100 μ M	≥ 100 μ M (low toxicity)
Wild type	102.6	107.2	105.8	105.1
SPY50780	106.1	108.3	108.8	105.5
<i>CLN2_{oe}</i>	101.7	103.7	104.6	104.8
<i>mgt1</i>	102.7	106.6	106.5	105.0
<i>mec2</i>	105.4	107.3	105.8	106.0
<i>mlh1</i>	103.8	107.2	105.9	104.5
<i>rad14</i>	103.9	107.4	106.5	106.4
<i>bub3</i>	104.8	106.0	106.8	106.0
<i>rad50EPP</i> [‡]	102.2	105.3	106.3	107.7
<i>sgs1</i>	103.3	106.7	106.8	104.8
<i>rad52</i>	103.6	106.8	105.9	104.0
<i>rad18</i>	103.9	106.2	106.5	106.6
<i>rad50</i>	102.9	105.5	104.4	104.7
Σ (mean \pm SEM) [‡]	103.6 \pm 0.18	106.6 \pm 0.18	106.2 \pm 0.20	105.5 \pm 0.17

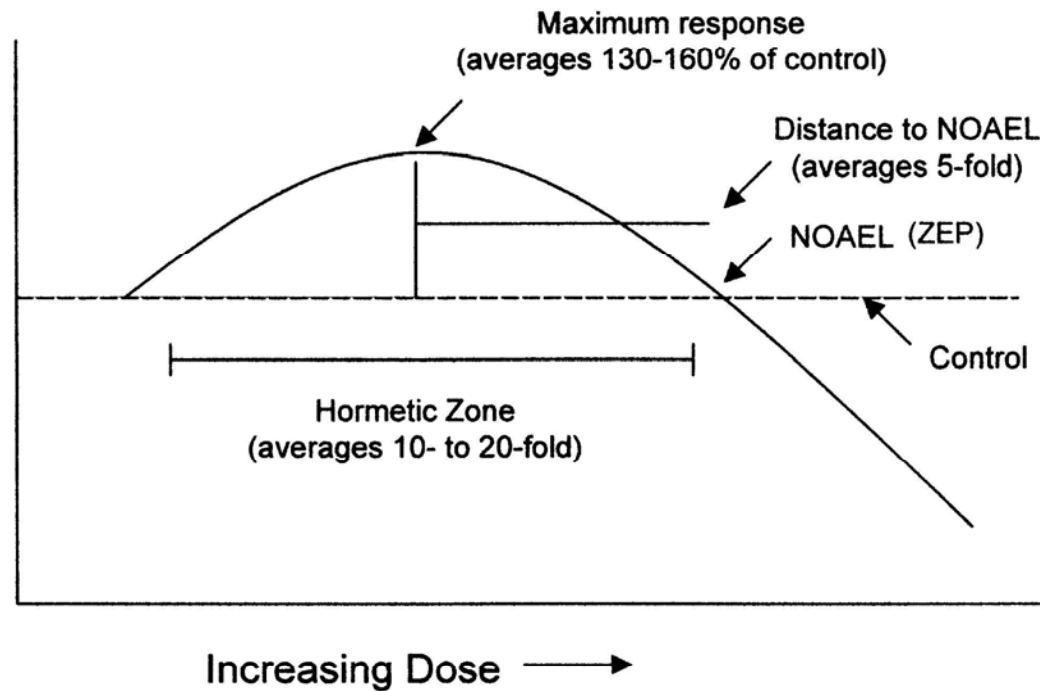
[†] "Highest nontoxic dose" = Benchmark Dose (BMD) \approx NOAEL \approx ZEP.

[‡] Overall mean (Σ) based on >4500 responses for each dosage range.

Adapted from E.J. Calabrese, J.W. Staudenmayer, E.J. Stanek, G.R. Hoffmann
Toxicological Sciences 94: 368-378, 2006.

Hormesis

Characteristics of Inverted U Dose-Response Curve



E.J. Calabrese, *Crit. Rev. Toxicol.* 35:463-582, 2005.

Areas of Debate about Hormesis

Philosophical questions related to the hormesis concept.

Scientific issues that generate debate about hormesis.

Political & ethical issues that are a source of controversy.

Philosophical Questions Related to the Hormesis Concept

Is there epistemological justification for the hormesis concept?

Do the diverse manifestations of hormesis obfuscate conceptual clarity?

Are operational definitions paramount for policy applications?

How does the hormesis concept relate to central biological principles?

Scientific Issues in the Debate about Hormesis

Impediments to detecting and measuring hormesis.

Apparent hormesis arising as an artifact.

Difficulties in using the scientific literature to determine the prevalence of hormesis.

Paucity of experiments specifically designed to evaluate whether responses are hormetic.

Insufficient understanding of mechanisms.

Impediments to Detecting Hormesis

Being a low-dose phenomenon hinders its evaluation.

Differences from control / background levels are modest.

Statistical power limits most studies.

Data that appear to be hormetic may not exclude other models.

Apparent Hormesis Arising as an Artifact

Pooling endpoints can create an illusion of hormesis.

Atypical controls can make low doses seem hormetic.

Essentiality can mimic hormesis.

Difficulty of Evaluating Prevalence of Hormesis in Scientific Literature

Many studies do not permit an evaluation of low doses.

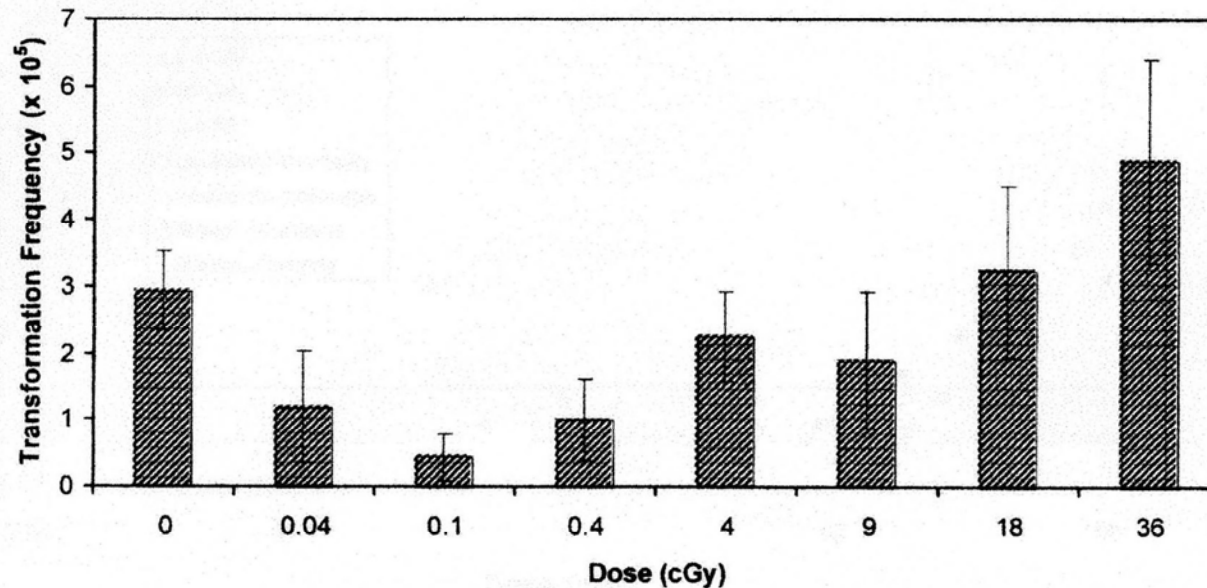
The choice of studies may introduce bias.

The existence of well-documented cases of hormesis does not establish prevalence.

Many reports of hormesis lack a clear denominator that defines prevalence.

Recent literature surveys have made progress in addressing these problems.

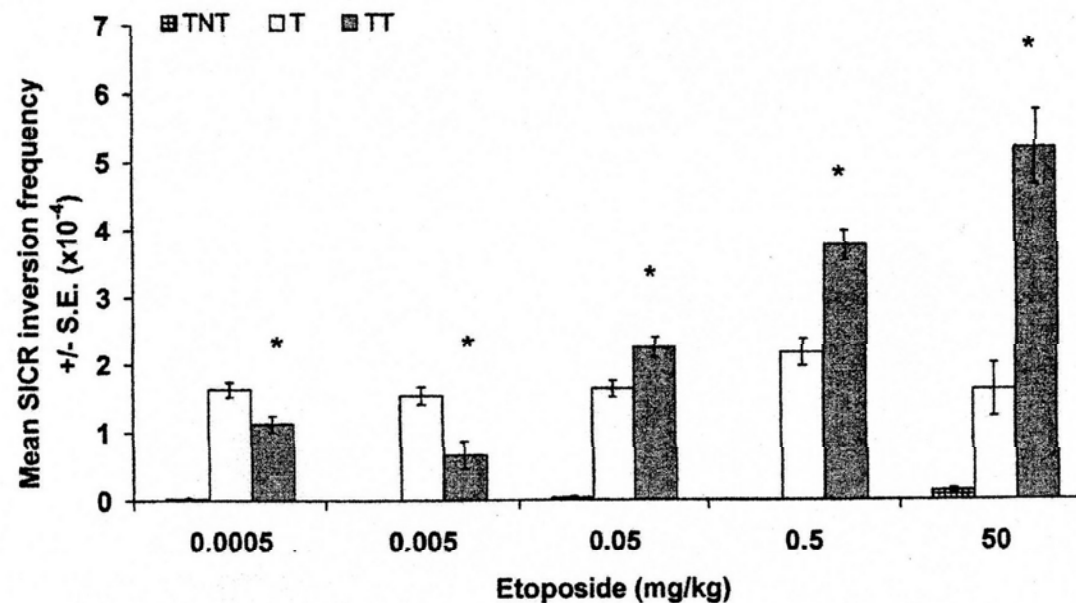
Induction of Neoplastic Transformation by X Rays in Cultured Human Cells



**HeLa x skin fibroblast hybrid cells treated with 60 kVp X rays
(transformation frequencies \pm 95% confidence intervals)**

J.L. Redpath, *Dose-Response* 4:302-308, 2006.

Induction of Somatic Intrachromosomal Recombination (SICR) by Etoposide: Chromosomal Inversions in Spleen of pKZ1 Mice



SICR was measured in pKZ1 transgenic mice after a single intraperitoneal injection (TT: etoposide; T: control; TNT: nontransgenic control for nonspecific staining).

A.M. Hooker, R. Horne, A.A. Morley, and P.J. Sykes
Mutation Research 500: 117-124, 2002.

Mechanisms Contributing to Hormetic Responses at Low Doses

Overcompensation to a disruption in homeostasis by overshooting homeostatic feedback controls.

Adaptive responses based on inducible repair processes.

Enhanced defenses against oxidative stress.

Activation of transcription factors; upregulation of genes for cytoprotective proteins, growth factors, and cytokines.

Interaction of exogenous agents with stimulatory & inhibitory receptor subtypes of endogenous regulatory systems.

Interactions among cell proliferation, cell-cycle delay, apoptosis, and DNA damage.

**Death of cells predisposed to spontaneous transformation;
Selective induction of apoptosis in transformed cells.**

Enhancement of gap junction intercellular communication at low doses but inhibition at high doses.

Enhanced immune responses.

Political and Ethical Issues Causing Controversy about Hormesis

Whether hormesis should influence risk assessment policies.

Conflation of science and policy.

Fear that recognition of hormesis can undermine protections of health and environment.

Unique implications of biphasic responses.

Linkages of hormesis to ethical principles.

Accommodating sensitive subpopulations.

Questions Concerning Possible Applications of the Hormesis Concept

Should hormesis influence policy related to low-dose risks?

How do the following factors affect viewpoints on hormesis in relation to policy?

- Divergent perceptions of benefit and risk associated with a hormetic response.**
- Belief that policy decisions should be based on the best available science.**
- Ethical principles.**
- Practicality of assimilating hormesis into the estimation of hazards.**

Divergent Perceptions of Benefit & Risk Associated with a Hormetic Response (In Order of Perceived Risk)

Hormesis should be assimilated into risk assessment. Public health would benefit from regulation to the hormetic zone.

Low-dose risks are probably smaller than often thought, but application to policy is premature.

Prudence argues for steering further from the brink of toxicity. The danger of misidentifying the boundaries of hormetic and toxic zones outweighs a modest hormetic benefit.

Hormesis suggests proximity to the toxic zone and should be taken as a warning. The hormetic zone should be avoided, as effects may differ among endpoints and individuals.

Policy Decisions and the Best Available Science

Adherence to an incorrect model as if it were true is not in the interest of science or policy.

Accepting a model for scientific interpretation does not necessitate its use for policy.

Policy decisions should be made with cognizance of the best available science.

Denial of hormesis does not protect public health.

Relationship of Hormesis to Ethical Principles

Autonomy, nonmaleficence, beneficence, and justice.

Central principles in biomedical ethics:

- Nonmaleficence: avoiding the causation of harm.**
- Beneficence: conferring benefit.**

Threshold and linear models lend themselves to a single objective -- avoidance of harm.

Hormesis raises the possibility deriving benefit from the hormetic zone.

Regulating to a hormetic zone would entail a shift from nonmaleficence to beneficence.

Balancing nonmaleficence and beneficence with higher priority on the former.

Hormesis & Hazard Estimation

Information demands of regulating for hormesis.

Consequences of underestimating or overestimating hazards.

Consequences of ignoring or rejecting hormesis.

Heterogeneity in susceptibility to toxicants.

Consequences of Underestimating or Overestimating Hazards

Underestimating risk can lead to insufficient protection of public health & the environment.

Overestimating risk is often considered benign -- making errors on the side of safety.

Possible costs of risk overestimation:

- Excessive regulatory burden.**
- Hindered development of products & technology.**
- Avoidance of therapeutic or diagnostic benefits.**

Underestimation & overestimation of risk can both be detrimental.

Possible Consequences of Ignoring or Rejecting Hormesis

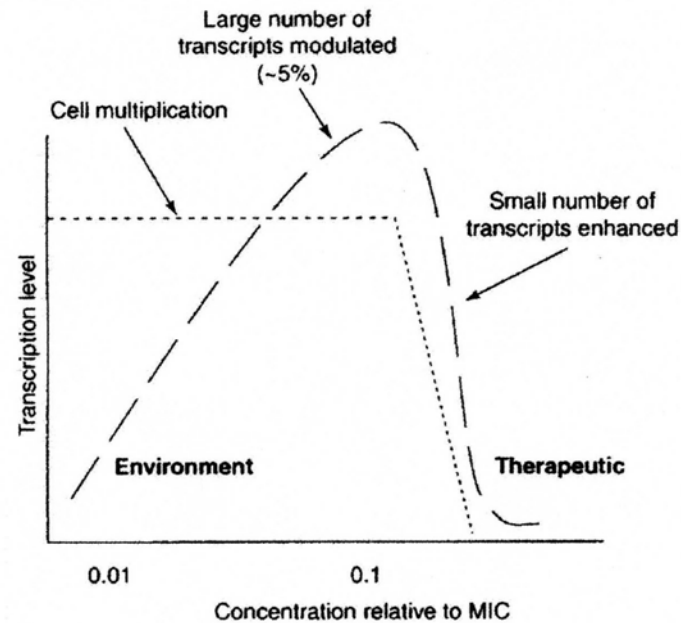
Less research on low doses, stress responses, and environmental implications of hormesis.

Retarded development of medical remedies that exploit natural adaptive responses.

Hindrance of recognition of hazards of the hormetic zone: hormetic stimulation of pathogens, tumors, and pests.

Possible loss of benefit of the hormetic zone.

Hormetic Effects of Antibiotics



“All antibiotics, regardless of their receptors and mode of action, exhibit the phenomenon of hormesis and provoke considerable transcription activation at low concentrations.”

Julian Davies, George B. Spiegelman, and Grace Yim
The world of subinhibitory antibiotic concentrations.
Current Opin. Microbiol. 9: 445-453, 2006.

Heterogeneity in Susceptibility to Toxicants

Differences among biological endpoints.

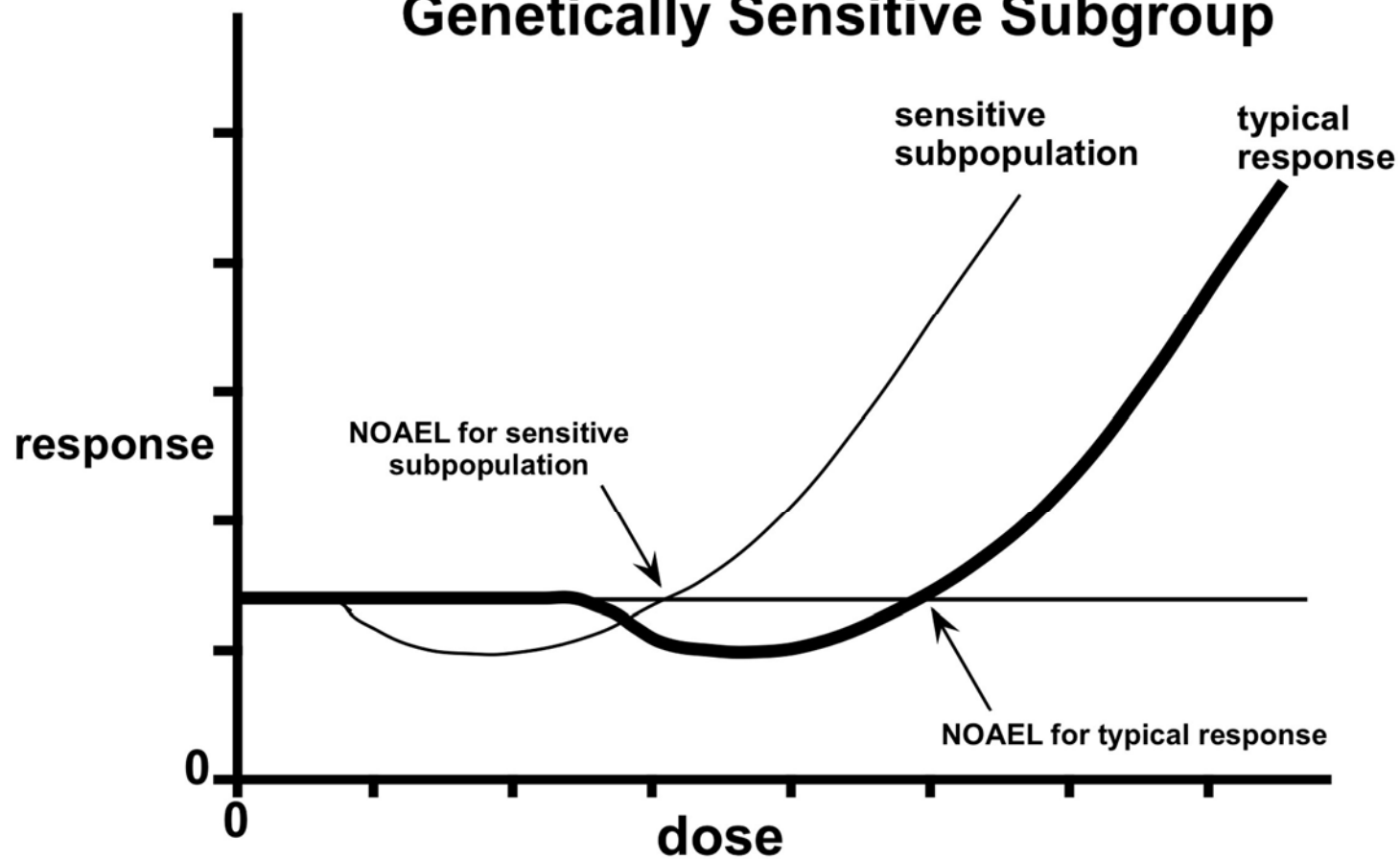
Differences among tissues and organs.

Differences among individuals:

- Genetic polymorphisms.**
- Susceptibility of different age groups.**
- Impaired health & altered susceptibility.**

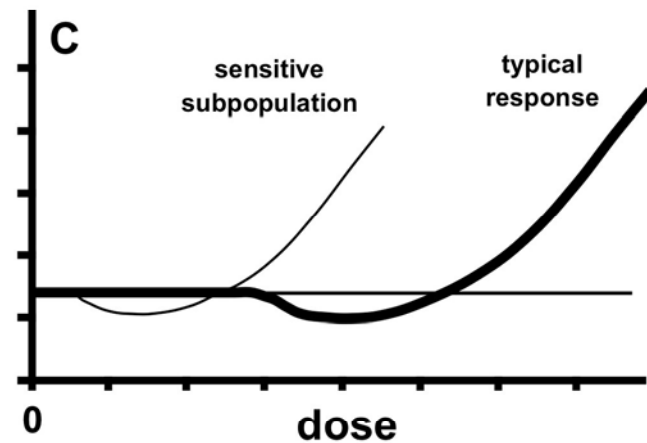
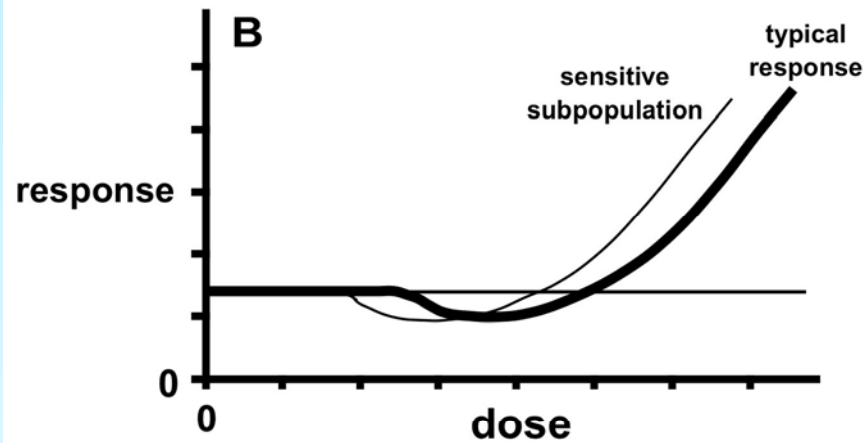
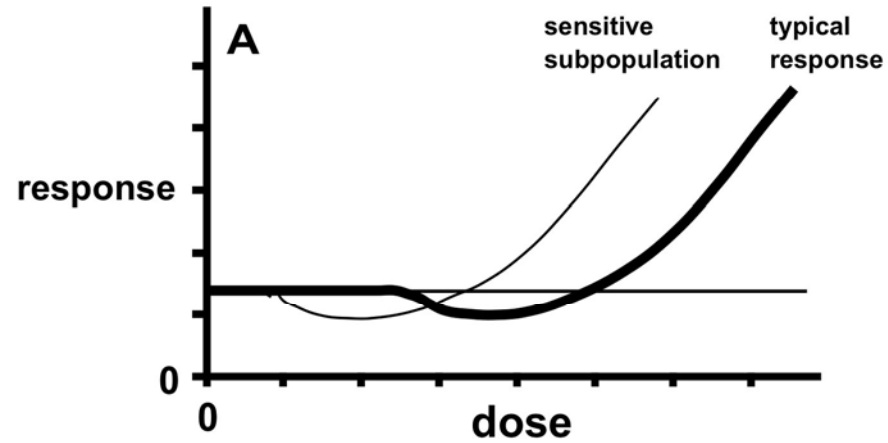
Species differences and environmental quality.

Hormetic Responses of a Typical Population and a Genetically Sensitive Subgroup



Hoffmann, G.R. and W.E. Stempsey. 2008. *Hum. Exper. Toxicol.*, in press.
(Available online in *BELLE Newsletter* 14 (3): 11-17, 2008)

Differences in Susceptibility: A Small Sensitive Subpopulation and the General Population



Accommodating Heterogeneity in Susceptibility to Toxicants

Sensitive groups must be accommodated under any dose-response model.

Biphasic curves pose questions of benefit and harm not encountered with monotonic responses.

The primacy of nonmaleficence in biomedical ethics gives high priority to protecting sensitive groups.

Sensitive species require consideration with respect to ecological effects of toxicants.

Complications of Hormesis

Observing J- or U-shaped curves requires that responses be measurable both above and below control levels.

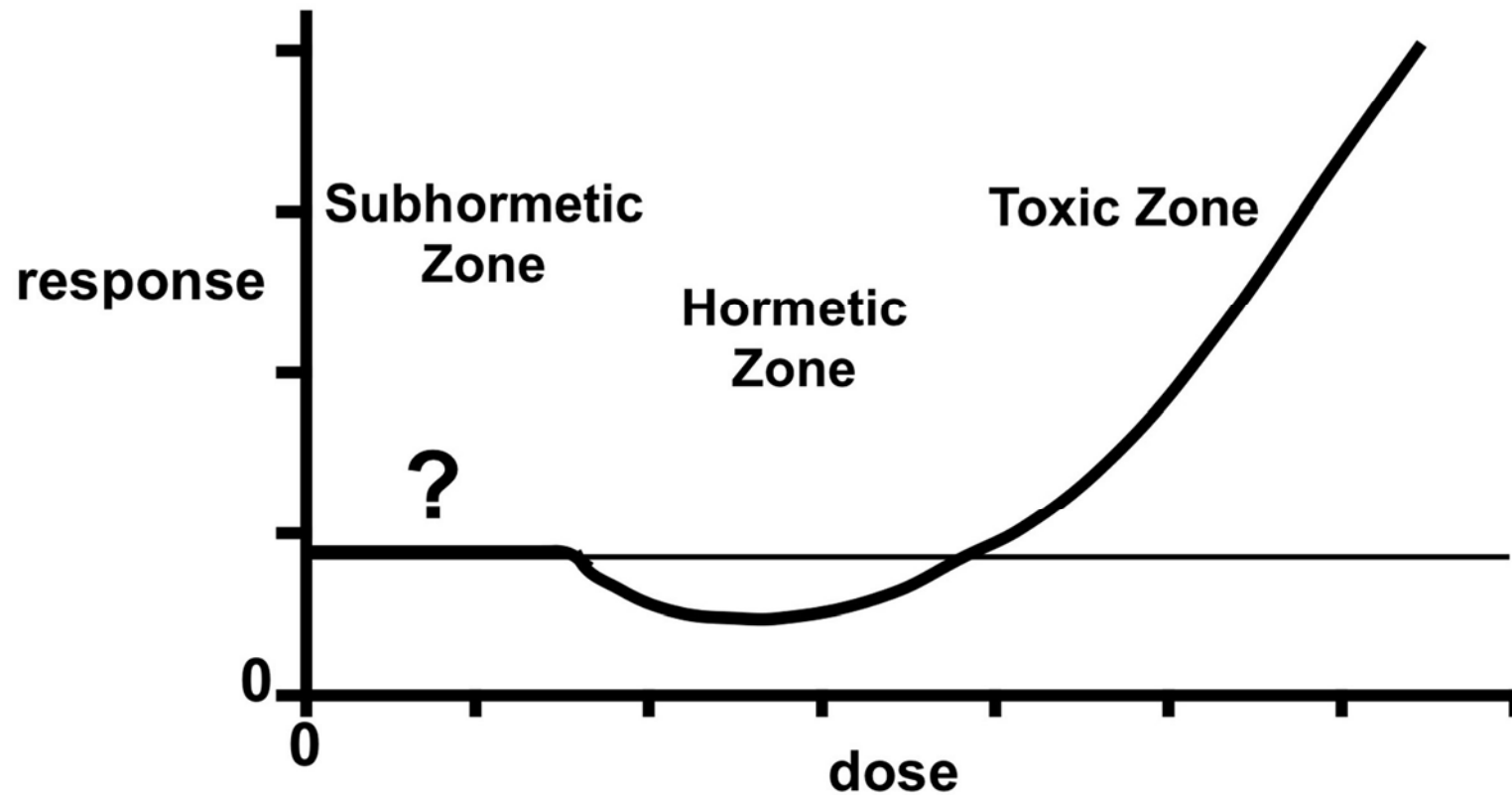
Some adaptive responses may not show hormetic curves for mechanistic reasons.

Hormesis cannot be observed if background exposures are already in the toxic zone.

The following are largely unresolved in relation to hormesis:

- Interactions among agents.**
- Nature of the subhormetic zone.**
- Temporal component of hormetic responses.**
- Nontargeted damage, bystander effects, genetic instability.**

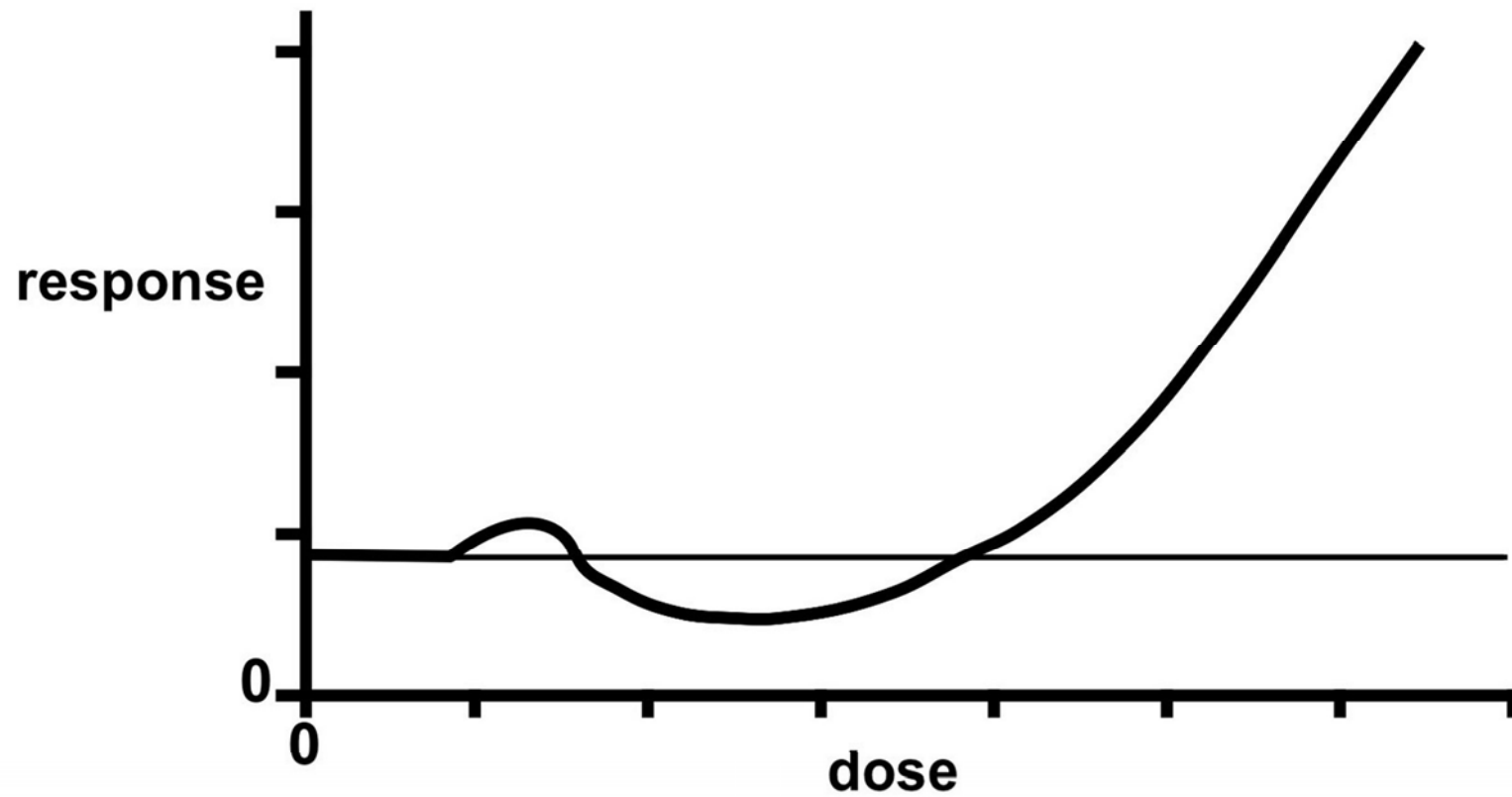
Hormesis (J-shaped curve)



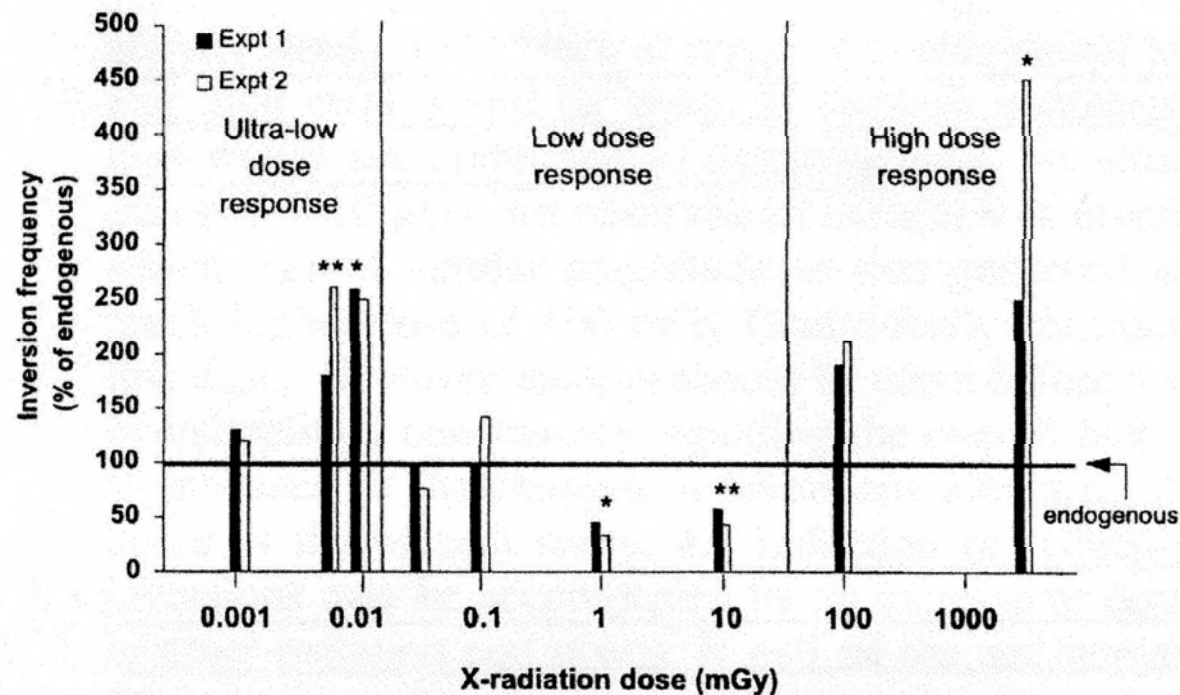
What is the shape of the dose-response
in the subhormetic zone?

Hormesis

Hypothetical Triphasic Curve



Induction of Inversions in pKZ1 Mice



Inversion frequency in pKZ1 mouse spleen after single whole-body exposure to x rays.

Figure from A.M. Hooker, M. Bhat, T.K. Day, J.M. Lane, S.J. Swinburne, A.A. Morley, & P.J. Sykes, *Radiation Research* 162:447-452, 2004.

Time Course of a Hormetic Response

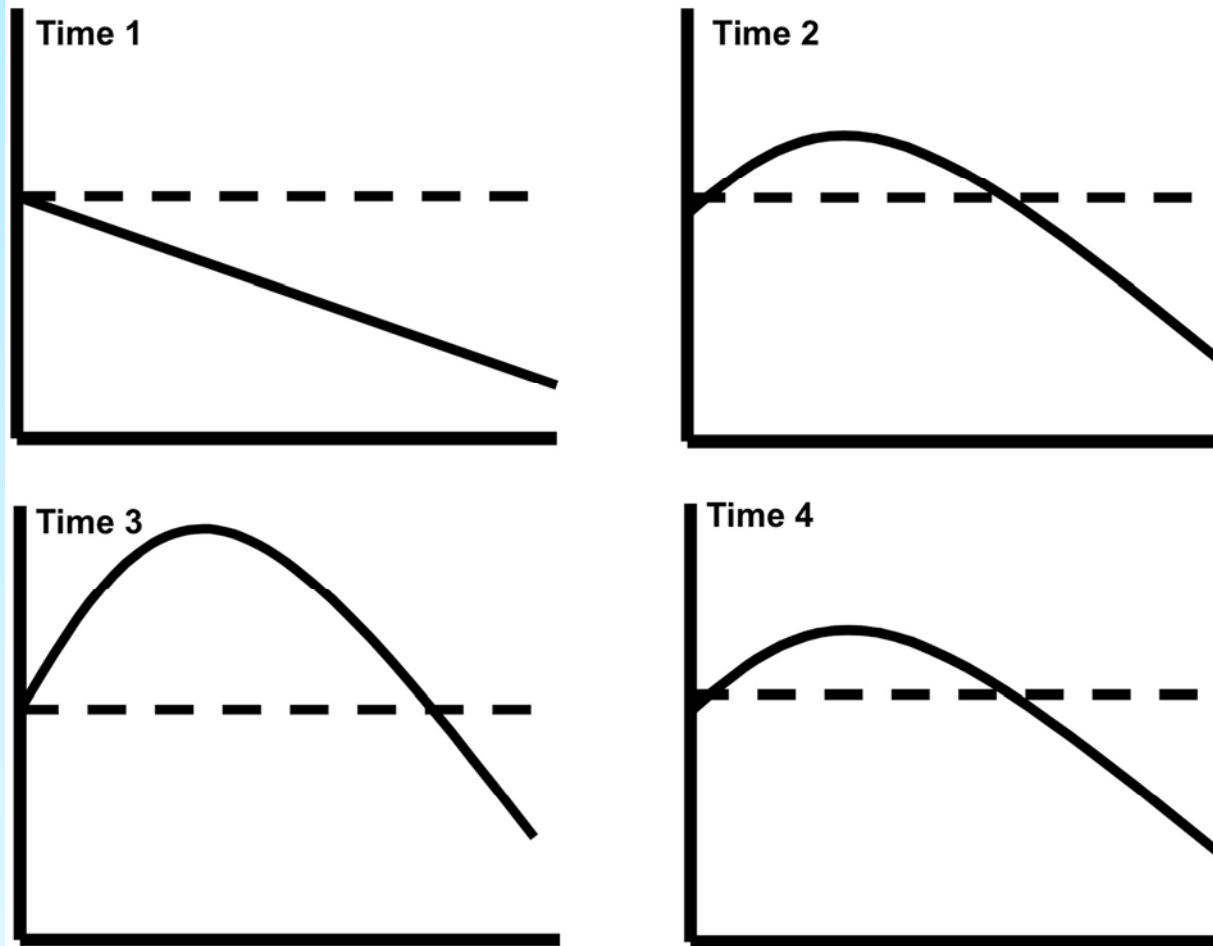


Figure adapted from E.J. Calabrese et al., 2007
Toxicology and Applied Pharmacology 222: 122-128.

Percent Apoptosis in Nonirradiated *src*-Transformed Cells after 65-h Coculture with Irradiated Normal (208F) Cells

Treatments and transformed-cell controls	Dose to normal cells (Gy)	Apoptosis in transformed cells (% \pm SD)
Control*	no normal cells	14.52 \pm 0.90
γ -Rays	0	26.70 \pm 1.54
	0.5	47.15 \pm 1.66
α -Particles	0	27.24 \pm 2.47
	0.5	48.69 \pm 2.24

* Unirradiated transformed cells in the absence of 208F cells.

Table based on D. I. Portess et al.
Cancer Research 67: 1246-1253, 2007.

Conclusions (-1-)

Growing evidence supports the reality and prevalence of hormesis.

The hormesis concept merits empirical evaluation and refinement independently of whether it is assimilated into policy on toxic substances.

It would be premature to regulate to the hormetic zone for chemical exposures now. How hormesis figures into policy needs to be revisited as risk assessment improves.

Using hormesis for regulatory purposes would require better understanding of the positions of the toxic and hormetic zones for diverse endpoints, tissues, individuals, and species.

Biphasic dose responses raise challenging ethical questions regarding sensitive subpopulations.

Conclusions (-2-)

Ecological effects of low doses and differences among species with respect to hormesis warrant continued investigation.

Effective exploitation of hormesis in medicine and agriculture is likely to precede its use in toxicologic risk assessment.

Deeper understanding of stress responses can stimulate medical and technological advances.

The hormesis concept has important implications for antimicrobial and cancer therapy.

Better understanding of hormesis can foster effective public health and environmental policies.