Chemical Hormesis

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2004 AIHCe Roundtable 243

Chemical Hormesis and Industrial Hygiene: Are We Over-Controlling Exposures?

- Edward J. Calabrese -- The Maturing of Hormesis as a Credible Dose-Response Model
- John Doull -- The Impact of Hormesis on the Evolution of Risk Assessment
- Michael Jayjock -- Hormesis and the Setting of Occupational Exposure Limits
- Gary E. Marchant -- Regulatory Applications and Acceptance of Hormesis
- Kenneth A. Mundt -- What Can Epidemiology Contribute to the Concept of Chemical Hormesis?
- Joseph V. Rodricks -- What Needs to Be Done if Hormesis is to Influence Public Policy?

nature

February 13, 2003

Dangerous levels of toxins miscalculated

Potential pollutants and poisons may be beneficial in low doses.

- September 2003

HORMESIS:

Nietzsche's Toxicology

- **Whatever doesn't kill you might make you stronger**

Science

October 17, 2003

- HORMESIS:
  Sipping From a Poisoned Chalice

June 9, 2003

A Little Poison Can Be Good For You

The received wisdom about toxins and radiation may be all wet.

The Boston Globe

December 12, 2003

A scientist finds benefit in small doses of toxins

AMHERST -- Edward J. Calabrese, a gray-haired man who works in a rundown office surrounded by documents on highly toxic chemicals, has an explosive idea.

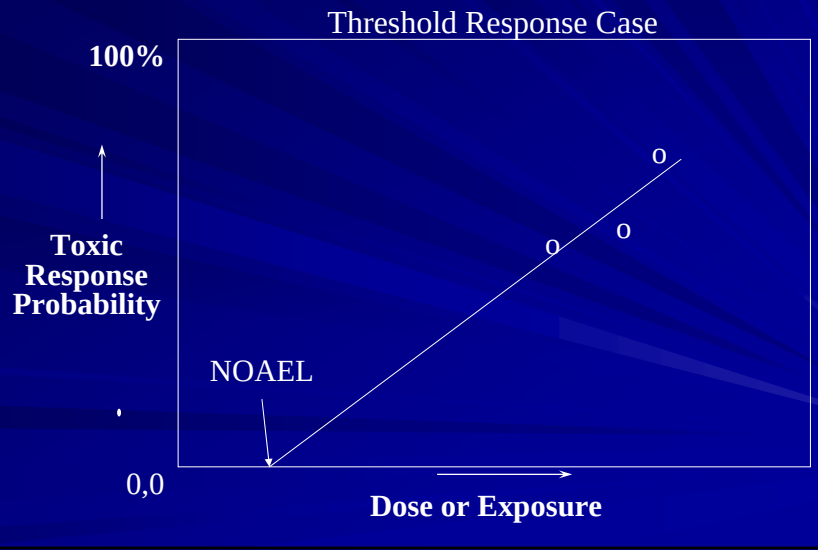
Dose-Response Assessment

The process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent.

Toxicity Assessment Noncarcinogenic Effects

- Threshold Response
- Can determine a no-effect level

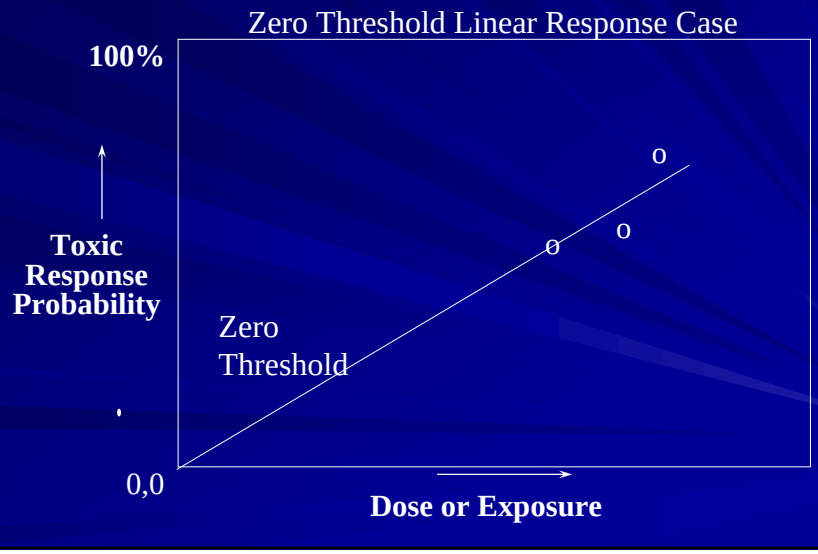
Dose-Response Curve



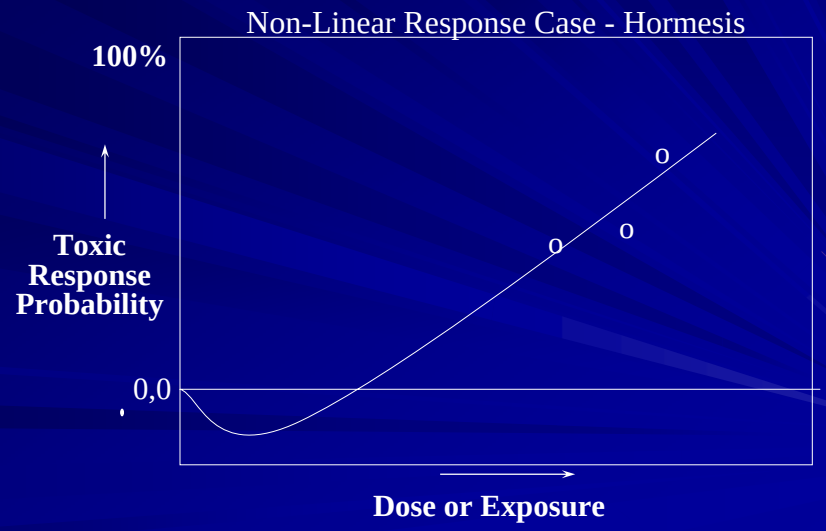
Toxicity Assessment
Carcinogenic Effects

- Nonthreshold response
- No dose is risk free

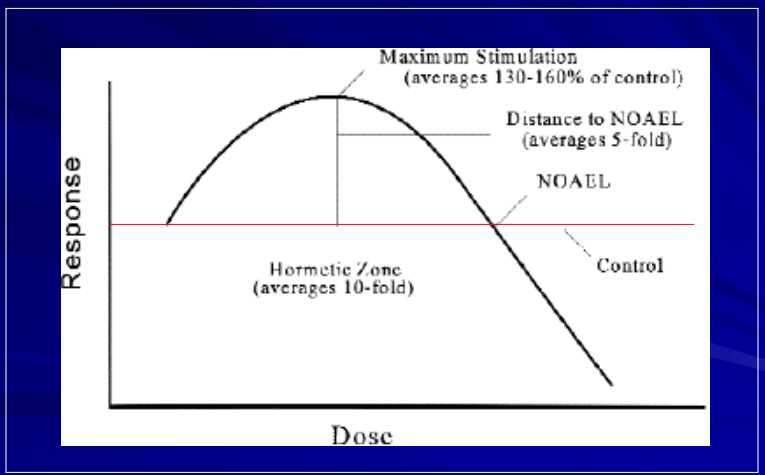
Dose-Response Curve



Dose-Response Curve



Hormesis Curve



Chemical Hormesis

- Calabrese, Edward J. and Baldwin, Linda A., "The Dose Determines the Stimulation (And Poison): Development of a Chemical Hormesis Database," *International Journal of Toxicology* **16:**545-559 (November-December 1997)
- Biological Effects of Low Level Exposure (BELLE) www.belleonline.com
- Low-dose stimulation/high-dose inhibition - Arndt-Schultz Law

Paracelsus

"What is it that is not poison? All things are poison and none without poison. Only the dose determines that a thing is not poison."

Definition of Hormesis

- Low-dose stimulation followed by higher dose inhibition.

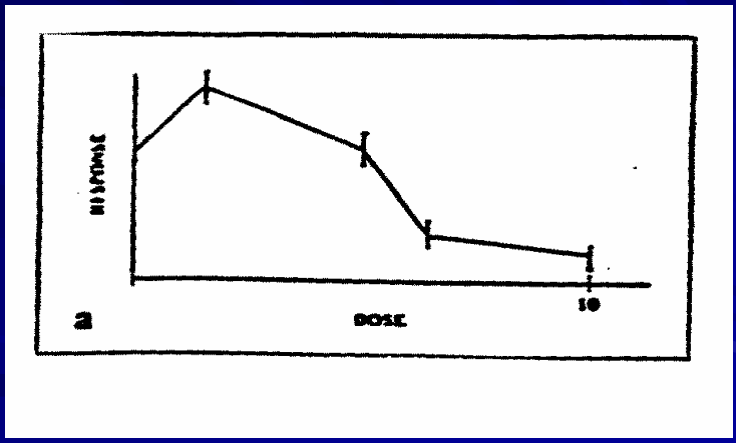
Criteria used to judge data for evidence of hormesis

- The magnitude of the low dose stimulatory response
- The number of doses establishing the reliability of the beta-curve
- Statistical power
- The reproducibility of the findings

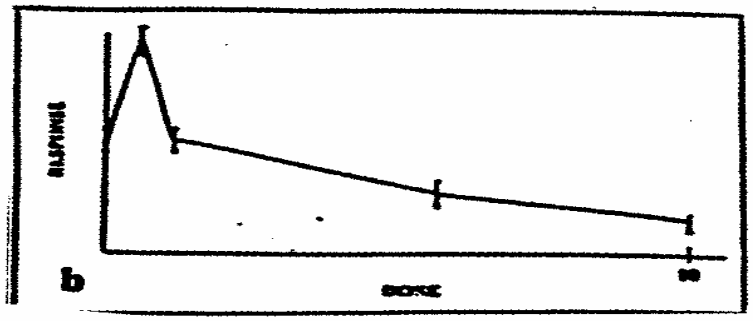
To evaluate high conformity to the beta-curve

- Establishment of an endpoint-specific lowest observed effect level (LOEL) and no-observed-effect level (NOEL)
- expected to have ≥ 4 doses distributed relative to the NOEL.

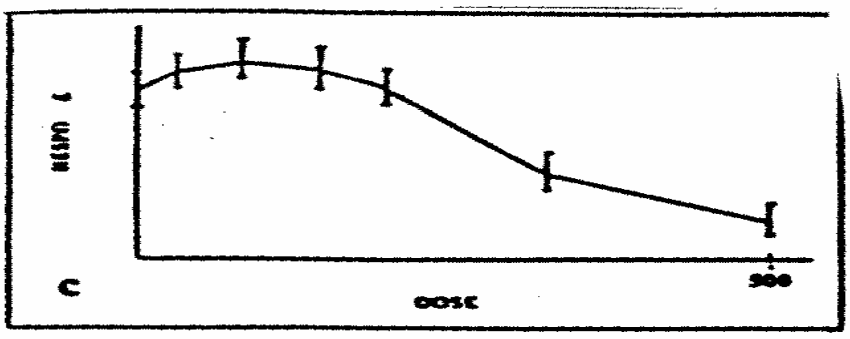
Toxicology Study Evaluation Example 1



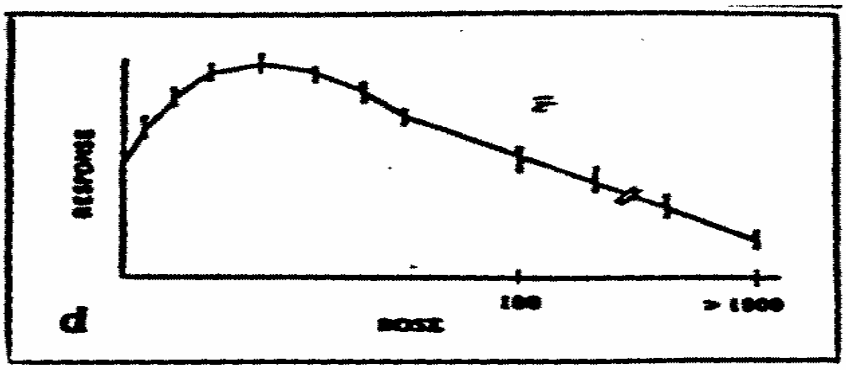
Toxicology Study Evaluation Example 2



Toxicology Study Evaluation Example 3

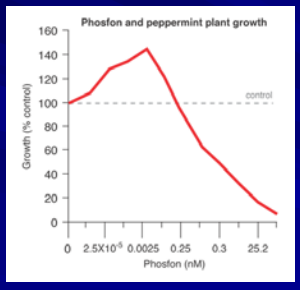


Toxicology Study Evaluation Example 4



Example 1

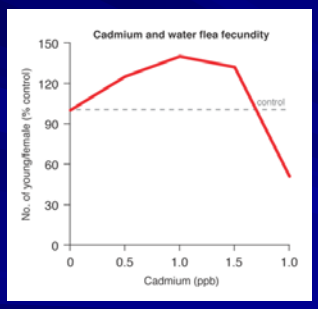
- Low doses of phosfon, a herbicide, caused plants to grow better



CALABRESE AND HOWE, *PHYSIOL. PLANT.* **37**, 163 (1976)

Example 2

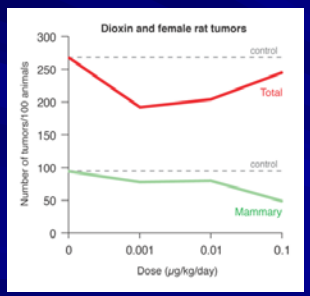
- A little cadmium causes water fleas to produce more young



BODAR *ET AL.*, *AQUATIC TOXICOL.* **12**, 301 (1988)

Example 3

- Small amounts of carcinogenic dioxin reduces tumors in rats



KOCIBA *ET AL.*, *TOXICOL. APPL. PHARMACOL.* **46**, 297 (1978)

Results of initial screening organized by agent

Agent	Percent
Alcohol and metabolites	6.2
Antibiotics	7.9
Auxin related	4.6
Hydrocarbons	3.4
Metals	29.6
Herbicides	7.2
Insecticides	6.1
Fungicides	1.5
Pesticides	2.9
Miscellaneous	30.6

Results of initial screening organized by endpoint

Endpoint	Percent
Growth	62.2
Metabolic Effects	15.2
Longevity	5.2
Survival	5.7
Reproduction	5.7
Miscellaneous	5.8

Results of initial screening organized by test model

Test Model	Percent
Bacteria	9.3
Protozoa	3.0
Fungi	6.4
Plants	34.9
Animals	46.3

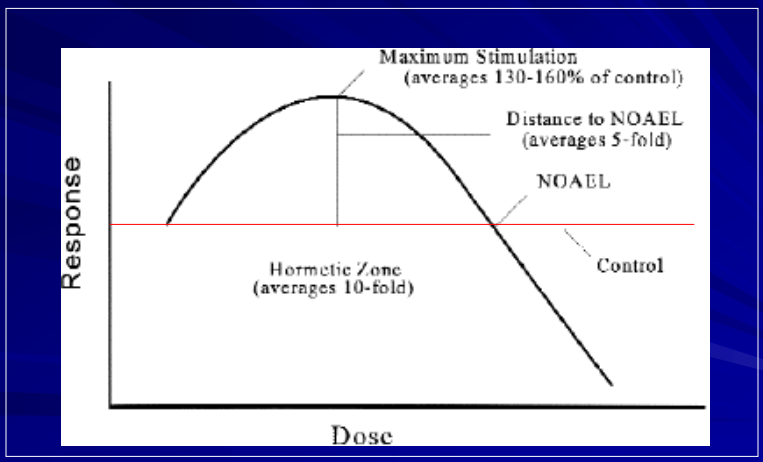
Generalizability of Hormesis

- Numerous species
- Broad range of chemical classes
- Broad range of biological endpoints

Assessing Characteristics of Chemical Hormetic Dose/Response Zone

- Data evaluated with respect to:
  - Dosage range of hormetic zone
  - Maximum stimulatory response
  - Magnitude of dosage difference from maximum to NOEL.

Hormesis Curve



If Hormesis Exists and Is Widely Generalizable, Why Is It Infrequently Observed?

- Study design
  - Influence of safety evaluation
  - Dose intervals
  - Not looking for non-adverse effects

A Priori Frequency of Hormesis

- Examined literature to determine the prevalence of hormesis.
- 3 journals
- Reviewed articles
  1. experimental data,
  2. used (non-dosed) controls,
  3. could show excess responses,
  4. had 2 doses at and/or below the NOAEL
  5. had at least one dose showing inhibition.

A Priori Frequency of Hormesis

- 20,285 articles screened
- 195 articles (1%) contained 668 relationships meeting entry criteria.
- 245 (37%) showed evidence of hormesis

Recent Titles

- Calabrese, E.J., Baldwin, L..A. “Hormesis: The dose-response revolution,” *Annu. Rev. Pharmacol.* 43: 175-197 (2003)
- Calabrese, E.J., Baldwin, L.A., “The hormetic dose-response model is more common than the threshold model in toxicology,” *Toxicol. Sci.* 71 (2): 246-250 (Feb. 2003)
- Calabrese, E.J., Baldwin, L.A. “Toxicology rethinks its central belief - Hormesis demands a reappraisal of the way risks are assessed,” *Nature* 421 (6924): 691-692 (Feb. 13, 2003)

Human Health Research Strategy for Improving Risk Assessment

A possibility that needs to be recognized and incorporated into the research on aggregate and cumulative risk is an awareness of potentially positive or adaptive biological responses associated with low-level exposures. It is anticipated that a U-shaped dose-response curve at low (environmentally relevant) concentrations of single and multiple compounds could be quite common …. This information could be exceedingly valuable in identifying practical thresholds of human response in defined populations which in-turn could speak to the potential impact of any risk management activity aimed at lowering human exposure. The panel suggests that nonmonotonic dose-response proximate to actual exposure levels is a potential outcome (hypothesis) that should be incorporated into this research.

Implications for Risk Communication

- Hormesis challenges past dogma.
- Toxic substances may be beneficial at low doses
- Hormesis seems like a chemical industry gimmick.
- Pollutants always characterized as harmful

Is the public ready for this?