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Hormesis in Regulatory Risk Assessment: Science and Science Policy

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Overview

- Science vs Science Policy
- How EPA Makes Science Policy
- Hormesis Science and Science Policy
- Looking Ahead

Defining Science Policy

- "Risk assessors might be faced with several scientifically plausible approaches (*e.g.*, choosing the most reliable dose-response model or extrapolation beyond the range of observable effects) with no definitive basis for distinguishing among them. The earlier Committee [NRC 1983 (The "Red Book")] pointed out that selection of a particular approach under such circumstances involves what it called a *science-policy* choice. Science policy choices are distinct from the policy choices associated with ultimate decision-making…"

Source: NRC 1994 Science and Judgement in Risk Assessment p 27

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Defining Science Policy

- Science Policy is policy about how science will be used to inform decisions
- Often focused on what choices to make in the face of scientific uncertainty
- May be guided by many factors such as concern about safety, equity, or burden of proof
- For U.S. EPA, science policy for risk assessment is often implemented through guidance documents

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Some Science Policy Choices

- Which study?
  - Epidemiology
  - Toxicology
    - Which species?
    - Which sex?
    - Which endpoint
- How to estimate exposure?
  - Measure?
  - Model? Which Model?
- How to estimate dose-response?

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Does The Model Matter?

- Cancer Risk from 3.45 ppb formaldehyde in air
  - assume breathe 20 cubic meters of air per day
  - assume 70 years of exposure
  - Assume population of 10,000,000

Model	Predicted Lifetime Cancers
One-hit	21,000
Multistage	<1
Probit	0

Separating Science and Science Policy

TESTIMONY OF

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BEFORE THE
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
SUBCOMMITTEE ON PUBLIC SECTOR SOLUTIONS TO GLOBAL WARMING, OVERSIGHT, AND CHILDREN'S HEALTH PROTECTION
UNITED STATES SENATE

May 7, 2008

"Science informs, and provides a foundation for, EPA's regulatory decisions. At the same time, it is important to recognize that what often appear to be purely scientific questions or assessments generally involve both "science" and "science-policy" considerations. For example, **developing risk values requires many decisions, choices, and assumptions that are generally guided by Agency science policy**."

"Because the scientific method encourages critical thinking and professional disagreement, it does not commonly lend itself to a "bright line" that decision-makers can use as a reliable reference point. A range of reasonable and scientifically defensible options or decisions are usually available, and there is rarely a single "best answer" for use in decision-making. Scientific assessments also entail varying degrees of uncertainty and many decisions, choices, and assumptions must be made based on science-policy considerations"

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EPA's Science Policy Council

The Science Policy Council (SPC) serves as a mechanism for addressing EPA's many significant science policy issues that go beyond regional and program boundaries. With a goal of integrating policies that **guide Agency decision-makers in their use of scientific and technical information**, the SPC works to implement and ensure the success of selected initiatives recommended by external advisory bodies such as the National Research Council and the Science Advisory Board as well as others such as the Congress, industry and environmental groups, and Agency staff. In this way, the SPC contributes guidance for selected EPA regulatory and enforcement policies and decisions.

Source: http://www.epa.gov/spc/

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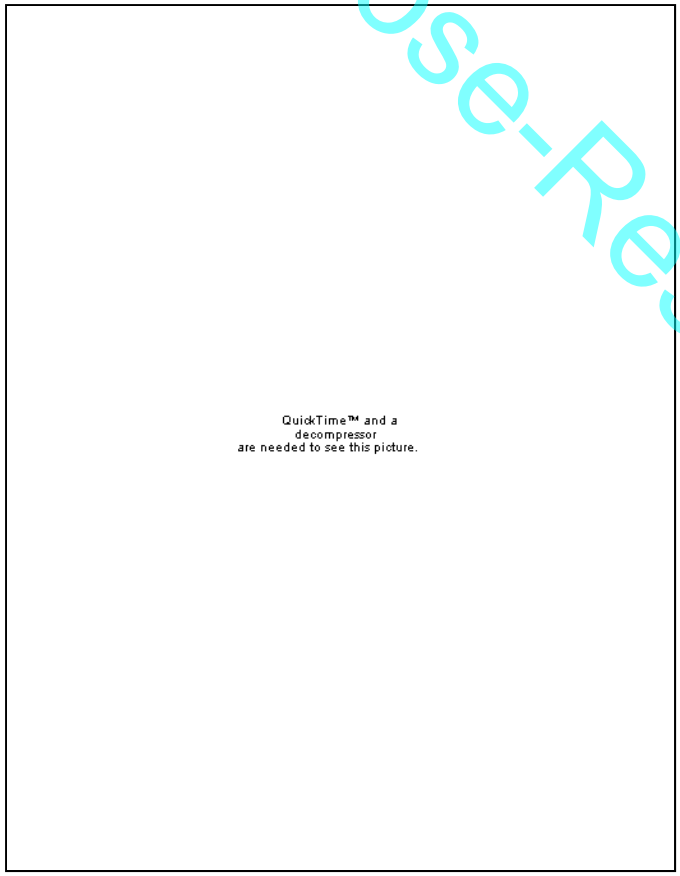
Science vs. Science Policy



"Importantly, remember that risk characterization is not just about science. It makes clear that science doesn't tell us certain things and that science policy choices must be made." Page 11

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Science Policy and Dose-Response

- "**It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach provides adequate public health conservatism** in the absence of chemical-specific data indicating differential early-life sensitivity or when the mode of action is not mutagenic" Page 1-19

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Sample EPA Hormesis Science

- Grants mentioning hormesis
  - Development of Biomarkers for haloacetonitriles-induced cell injury in Peripheral Blood - Ahmed Elsayed Ahmed, UT Medical Branch, Galveston
  - Development of a BBPK Model for the Thyroid Axis in the Pregnant Rat and Fetus for the Dose Response Analysis of Developmental Neurotoxicity - Jeffrey W. Fisher , Duncan Ferguson, John Wagner, University of Georgia

- Issues and Applications in Toxicology and Risk Assessment (Toxicology Conference, April 3-26, 2001) – Hormesis in Human Health and Ecological Risk Assessment

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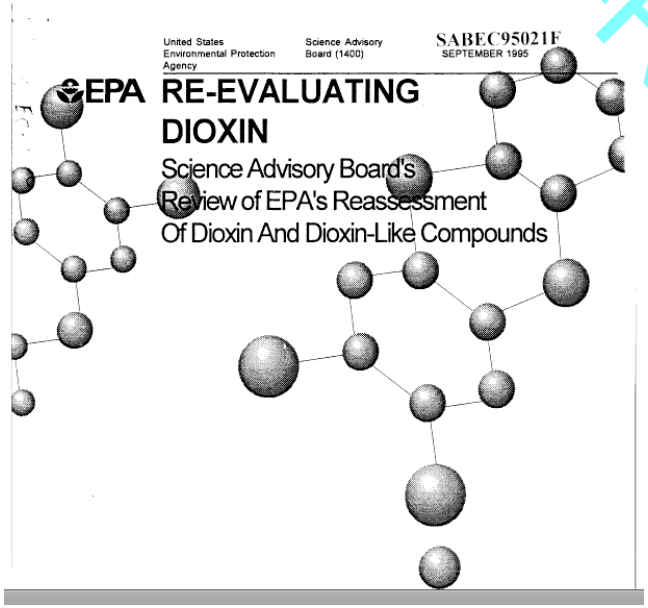
Science Advice on Hormesis



The Committee urges EPA to examine fundamental principles of receptor theory, and the evidence from the epidemiological and toxicological data bases in the low exposure ranges for their consistency with its assumption of a linear, non-threshold carcinogenic risk. In addition, the Committee (with several exceptions) believe that the Agency should at least consider the suggestions from the public[28] regarding evidence for reduced cancer risks associated with very low levels of exposure. Although such a concept seems to be counterintuitive, there is a body of literature (albeit debatable, and both pro and con) on the concept of hormesis and ionizing radiation biological effects; this concept was not discussed during the review meeting, but is mentioned as a possible area of future investigation.[29]

[29] Several Members of the Committee believe that the evidence of "hormesis" for dioxin-like compounds is not statistically or experimentally significant at this time, and that until more solid evidence is obtained, this issue is irrelevant. These Members also contend that the putative "hormesis" effects are occurring at the levels of exposure at which the developmental and immunological alterations are seen.

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Science Dissent

Review

Hormesis and Its Place in Nonmonotonic Dose–Response Relationships: Some Scientific Reality Checks

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OBJECTIVE: This analysis is a critical assessment of current hormesis literature. I discuss definitions, characterization, generalizability, mechanisms, absence of empirical data specific for hormesis hypothesis testing, and arguments that hormesis be the "default assumption" in risk assessment.

DATA SOURCES: Hormesis, a biological phenomenon typically described as low-dose stimulation from substances producing higher-dose inhibition, has recently garnered interest in several quarters. The principal sources of published materials for this analysis are the writings of certain proponents of hormesis. Surprisingly few systematic critiques of current hormesis literature exist. Limits to the phenomenon's appropriate role in risk assessment and health policy have been published.

DATA SYNTHESIS: Serious gaps in scientific understanding remain: a stable definition; generalizability, especially for humans; a clear mechanistic basis; limitations in the presence of multiple toxic end points, target organs, and mechanisms. Absence of both arms-length, consensus-driven, scientific evaluations and empirical data from studies specifically designed for hormesis testing have limited its acceptance.

CONCLUSIONS: Definition, characterization, occurrence, and mechanistic rationale for hormesis will remain speculative, absent rigorous studies done specifically for hormesis testing. Any role for hormesis in current risk assessment and regulatory policies for toxics remains to be determined.

KEY WORDS: bidirectional dose response, biphasic dose response, hormesis, nonmonotonic dose response. *Environ Health Perspect* 115:500–506 (2007). doi:10.1289/ehp.9619 available via *http://dx.doi.org/* [Online 4 January 2007]

The last decade has witnessed a revival of interest by some in hormesis, a biological phenomenon broadly defined as a "stimulatory" response to low doses of a substance that otherwise causes inhibition of response at higher doses (e.g., Calabrese and Baldwin 2002a).

Hormesis is a type of dose–response relationship, of which two general forms exist. Monotonic dose–response (MDR) relationships describe responses that proceed unidirectionally from zero dose or doses above zero. Nonmonotonic dose–response (NMDR) relationships show biphasic or bidirectional responses to dose, appearing in U-shaped or inverse U-shaped graphic forms. Graphic depictions of these responses appear in a number of articles (e.g., Calabrese and Baldwin 2001a, 2001b, 2001c; Davis and Svendsgaard 1994).

Hormesis in its current form has had surprisingly little systematic scientific scrutiny or collective peer review. Thayer et al. (2005) evaluated the relative merits and limits of hormesis as the "default assumption" for human health risk methodologies and associated policies. They identified lack of a mechanistic footing, questionable interpretations of hormetic data, and underestimation by proponents of the complexity and diversity of human population response to xenobiotic exposures.

The specific scientific framing questions for hormesis in this analysis are as follows:

- What is a coherent and valid working definition for hormesis?
- What is its generalizability?
- What is the evidence for or against hormetic phenomena in humans?
- Has any general underlying mechanism been adequately documented?
- What are limits to borrowed mechanisms?
- Can typical single end point hormesis accommodate multiple toxic end points, target organs, and toxicologic mechanisms?
- Is hormesis a valid default assumption in human risk assessment and exposure reduction policies?

Defining Hormesis

Hormesis has been plagued by absence of a stable definition. First, development of a definition has been an ad hoc process, with backing and filling over time. This ad hoc process has not been shaped by hypothesis testing but by the persistent search for, and analysis of, existing bodies of data [see Calabrese and Baldwin (2002a) for a current definition and its changes over time].

Definitions of hormesis also arose with little disciplinary consensus in relevant fields from expert committees using objective, arms-length approaches and guidelines.

Calabrese and Baldwin (2002a) define hormesis comprehensively as

> an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced (i.e., direct stimulation hormesis [DSH]) or the result of compensatory biological processes following an initial disruption in homeostasis (i.e., overcompensation stimulation hormesis [OCSH]).

There are still differences of opinion on this definition. It is largely driven by speculation and difficult to test empirically at present (Kitchin 2002; Pickrell and Oehme 2002). Others question the appropriateness of the term "hormesis" to cover all low-dose responses (Chapman 2002). "Direct" stimulation, one-half the definition, is descriptive only and lacks a mechanism. Overcompensation stimulation linked to preservation of homeostasis is offered as the mechanism of hormetic action.

Proponents of hormesis often attach the notion of "benefit" to hormesis. If an adverse effect has the dose–response curve going one way, then the opposite direction is deemed beneficial. This is argument by anomaly rather than by empirical evidence. The Calabrese and Baldwin (2002a) definition uncouples "benefit" from hormesis, given that hormesis is not inherently "beneficial" and can be deleterious to health. Anticancer drug actions that inhibit tumorigenesis in the normal dose–response range may be preceded by tumor cell proliferation, that is, an adverse end point, at low doses (Calabrese 2005a). Some still believe that hormetic responses are typically beneficial (Calabrese 2005b; Eaton and Klaassen 2003).

What Is Its Generalizability?

Various articles by Calabrese and Calabrese and Baldwin [see Calabrese (2005b) for citations] traced the early history of what is known as hormesis and claim it was "marginalized" unfairly. These authors assert that early 20th century research established hormesis sufficiently to warrant scientific acceptance but for unfavorable biases from influential scientists and linkage to homeopathy. Other claimed impediments are the evolution of risk assessment models favoring the high-dose realm of dose responses and public pressures for dealing with high-dose not low-dose exposures.

Review of the cited studies yields little convincing evidence that a strong earlier bias existed. More prosaic reasons likely applied. First, it would be reasonable to expect that experimental anomalies would garner less

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I thank J.M. Davis for a number of discussions and B. Mushak for editing assistance.

The author declares he has no competing financial interests.

Received 16 August 2006; accepted 4 January 2007.

CONCLUSIONS: Definition, characterization, occurrence, and mechanistic rationale for hormesis will remain speculative, absent rigorous studies done specifically for hormesis testing. Any role for hormesis in current risk assessment and regulatory policies for toxics remains to be determined.

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Science/Policy Dissent

Fundametal Flaws of Hormesis for Public Health Decisions.

Kristina A. Thayer, Ronald Melnick, Kathy Burns, Devra Davis, and James Huff

- *The concept of hormesis is based largely on empirical observations and does not adequately consider underlying mechanism(s) of action.*
- *Stimulatory responses are not always beneficial, and some may be harmful.*
- *Health decisions based on beneficial effects must address all the induced effects by that agent.*
- *Health decisions based on beneficial effects must address interindividual differences in exposure and susceptibility, including genetic, life-stage, and health status factors.*
- *Health decisions based on beneficial effects must address the fact that other environmental and workplace exposures may alter the low-dose response of a single agent.*

The claims and projections of health benefits from exposures to environmental toxicants and carcinogens are based on untested assumptions and **disregard numerous well-established scientific principles that underpin a public health-protective approach to regulating exposure to toxic substances**. If hormesis were used in the decision-making process to allow higher exposures to toxic and carcinogenic agents, this would substantially increase health risks for many, if not most, segments of the general population

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Where are We Today?

- No mention of hormesis in any EPA risk assessment guidance document
  - Guidelines for Cancer Risk Assessment
  - Guidelines for Developmental Toxicity Risk Assessment
  - Guidelines for Neurotoxicity Risk Assessment
- Hormesis is not explicitly excluded but no direction given on how to incorporate it into an assessment

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Why is Hormesis Shut Out?

- Science
  - Questions as raised by Mushak and Thayer *et al*.
  - Evidence from epidemiology?

- Science Policy
  - Seen as “not health protective”
  - Allow higher exposure to “toxic” materials
  - No evidence that ignoring hormesis is leading to bad decisions

Hormesis and "Public Health Conservatism"

"Some evidence suggests that many toxic agents that are harmful at high levels are actually beneficial at low levels. Thus, hormesis is a dose-response relationship in which low doses stimulate desirable effects and high doses inhibit them. **When hormesis is involved, use of a linear dose-response curve, with out safe thresholds, will actually cause mortality and morbidity effects.** Which default approach to the dose-response curve is precautionary? To raise this question is not to take any stand on whether some, many, or all toxic agents are beneficial or instead harmful at very low doses; it is only to say that the simultaneous possibility of benefits at low levels and of harms at low levels makes the precautionary principle paralyzing."

Source: CASS R. SUNSTEIN BEYOND THE PRECAUTIONARY PRINCIPLE (2003) UNIVERSITY OF PENNSYLVANIA LAW REVIEW Vol. 151: 1003-1058

What Might Change Things?

- Decision-focused risk assessment as advocated in NRC *Science and Decisions* report
- Weighing options changes approach to assessment
  - Do assessment to inform choices
  - Risks on each side of choice
  - Want “best estimates” of risk, not “health protective” with unknown (and often different levels of) conservatism

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What Might Change Things

- A clear public health case that not considering low dose non-monotonicity is a public health threat

- I don’t see any examples on the horizon, do you?

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Summary

- Risk assessment is a mix of science and science policy
- There are still science questions regarding hormesis and the way it should inform risk assessment
- Acceptance of hormesis in science policy choices only partly informed by advances in science - still need to contend with the premise that it is not “health protective”

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Thank You!