

# Hormesis: Once Marginalized, Evidence Now Supports Hormesis as the Most Fundamental Dose Response

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**Abstract** The biomedical community made a fundamental error on the nature of the dose-response relationship early in the 20th century and has perpetuated this error to the present. The error was the byproduct of the conflict between homeopathy and traditional medicine. To deny support to homeopathy, leaders of the biomedical community rejected the hormetic biphasic dose-response model, the proposed explanatory principle of homeopathy. The threshold dose-response model was adopted as an alternative model, quickly becoming central to toxicology/pharmacology and their numerous applications. Despite its near-universal acceptance, no attempt was made to validate the ability of the threshold model to accurately predict responses in the below-threshold zone at the time of acceptance and throughout the 20th century. In contrast, the hormetic biphasic dose-response model became marginalized and was excluded from the mainstream of pharmacological/toxicological teaching and practice, textbook development, professional society journal publications, annual meeting presentations, grant funding, and use in government risk assessment. Over the last decade there has been a resurgence of interest in hormesis due to findings indicating that hormetic responses are common, reproducible, and generalizable, as well as independent of biological model, endpoint, and chemical class/physical stressor. Large-scale studies have indicated that the threshold model fails to accurately predict responses below the threshold, whereas the hormetic dose-response model performs very well. These findings indicate that the biomedical community made an error on the nature of the dose-response relationship, compromising the accuracy of toxicological and risk assessment practices, including environmental exposure standards, and impeding drug discovery/development and drug safety studies.

**Keywords** Hormesis · Hormetic · Biphasic · U-shaped · J-shaped · Dose-response relationship · Adaptive response · Preconditioning · History of science

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## Introduction

The dose-response relationship is the central concept within the fields of pharmacology and toxicology. It guides how studies are designed and biostatistical modeling is performed, the general focus of mechanistic research, drug efficacy and safety evaluation, and governmental environmental risk assessment practices for protecting humans and other life against threats to food, water, air, and soil. The dose-response relationship is also a fundamental concept of biology, in that it is central to evolutionary theory and its underlying processes of mutation, DNA repair, and a plethora of integrative adaptive responses. Central to the biological and health sciences, the dose-response relationship is a scientific concept that seems as obvious as it is profound, being nearly universally understood based on common experience. Therein lies the trap into which the general public and the scientific community have fallen.

Over the last century the scientific community accepted the threshold dose-response model as a description of how chemical and physical stressor agents affect the vast range of biological processes across essentially all forms of life and biological organization. This concept has become integrated into all biological disciplines and regulatory practices, quietly evolving into a fundamental concept. Reinforcing this “scientific” decision on the primacy of the threshold dose-response model is the general recognition of thresholds in the physical sciences, such as melting, boiling, and freezing points, and common experiences with medications and other products. The convergence of agreement on the dose-response model by the scientific community and the general public is also as important as it is in reinforcing belief in the validity of this concept, hence its acceptance and status as a central pillar in various disciplines.

Despite the history of science with its self-correcting features and the wisdom of the general public’s experiences and its integration of perceptions concerning the dose-response relationship, both science and the lay public have the relationship wrong. This error has profoundly affected the understanding of evolutionary biology, the nature of the body’s adaptive response, and the testing and assessment of drugs and chemicals, adversely affecting the health of individuals and populations and even national and world economies due to misplaced priorities and extremely wasteful spending. The error originated in the fields of pharmacology and toxicology and, like a highly contagious disease, quickly infiltrated all biological disciplines, as well as government regulatory agencies, including their codified decisions with their non-self-correcting features. This error in judgment on the nature of the dose-response relationship became accepted in the early decades of the 20th century and has been perpetuated to the present time (Calabrese, 2005b, Calabrese, 2005c; Calabrese 2007; Calabrese and Baldwin, 2003a), reinforced by a dominant governmental regulatory and funding culture that strongly influences what scientific ideas will be studied.

This chapter assesses the history of the dose-response relationship and the basis of the error by the scientific community concerning it. The chapter proposes

the most basic and appropriate dose-response relationship for the biological sciences along with supportive documentation and a perspective on its broad societal implications.

## **Historical Antipathies, Rather Than Science, Determined Which Dose–Response Model Would Dominate Biology**

The error that determined what has been long considered the fundamental nature of the dose-response relationship was rooted in a scientific version of the Hundred Years' War, that is, the prolonged and bitter conflict between homeopathy and what eventually came to be called “traditional” medicine. To citizens of the late 20th and early 21st centuries, this “medical” conflict would seem to be a minor event, given the overwhelmingly powerful victory of traditional medicine, and therefore not likely to be more than a historical footnote. However, this will be shown not to be the case. As a result of this medical science-based conflict, the basic dose-response relationship—that is, the biphasic dose-response model—got caught in the cross-fire and was victimized because it was a central and highly visible feature of homeopathy.

The linking of the biphasic dose-response relationship to homeopathy was facilitated principally by Hugo Schulz (1853–1932), a professor of pharmacology at the University of Greifswald in northern Germany. Schulz believed that the biphasic dose responses (i.e., low-dose stimulation and high-dose inhibition) he observed in laboratory studies (Schulz, 1888) assessing the effects of chemical disinfectants on yeast metabolism could be broadly generalized and serve as the explanatory principle of homeopathy. Schulz [1923, with English translation by Crump (see Crump, 2003)] emphasized the reproducible nature of his findings in an autobiographic account of the discovery, a perspective that was strongly supported by detailed studies (Branham, 1929) specifically designed to reaffirm and generalize his findings to a wider range of potential antiseptic chemicals. Chester M. Southam and John Ehrlich (Southam and Ehrlich, 1943), forestry researchers at the University of Idaho who observed that low doses of extracts from the Red Cedar tree affected the metabolism of multiple fungal strains in a similar biphasic manner, renamed this dose response concept “hormesis” after the Greek word meaning “to excite.”

Prior to his intellectually transforming studies with yeasts, Schulz was educated and trained along a traditional biomedical path, with strengths in chemistry and pharmacology. He was also mentored by Eduard Pfluger, one of the founders of modern physiology. However, Schulz was quietly open to homeopathic principles and practices due in large part to an admired and respected family homeopathic physician friend with whom he had a long and intellectually engaged association (Bohme, 1986). At about the time (1882) that Schulz started his career at

Greifswald, research emerged indicating that veratrine, a homeopathic medicine, was a successful treatment for gastroenteritis. Because the causative bacteria had recently been identified and cultured, Schulz (Schulz, 1885) seized the opportunity to assess whether this drug acted via the killing of the bacteria. Extensive tests using a broad range of concentrations revealed that the drug was unable to do so. Although this observation failed to shake Schulz's belief in the efficacy of the drug, it did compel him to conclude that the drug must act via a mechanism other than cell killing.

Several years later when Schulz (Schulz, 1888) observed the biphasic concentration effects of a broad range of chemical disinfectants on yeast metabolism, he came to believe that he had determined how the veratrine might have been effective in the treatment of patients with gastroenteritis. That is, Schulz claimed that at low doses the drug could induce adaptive processes that permitted the person to resist the infection and facilitate recovery. He soon extended this hypothesis to the broader homeopathic field, believing that he had discovered the underlying explanatory principle of homeopathy.

Schulz quickly became a leader within the homeopathic community, devoting the remainder of his professional life to its further study and intellectual expansion. Because Schulz was well known in the pharmacological and medical communities, with numerous publications, as well as active participation on editorial boards of leading professional journals (e.g., *Naunyn-Schmiedeberg's Archives of Pharmacology*) (Starke, 1998), the homeopathic community looked to him to challenge traditional medicine in hopes of legitimizing their medical practices. This also meant that Schulz, his findings, and his interpretations became central in the conflict and the object of considerable criticism by those opposing homeopathic perspectives. The intellectual opposition, that is, traditional medicine, in the form of pharmacology and eventually its scientific offspring toxicology, could not accept Schulz's scientific findings because this would appear as an endorsement of homeopathy.

A careful analysis of Schulz's experimentation (Schulz, 1888) would have revealed that it was not directly relevant to homeopathic medical treatment theory and practice. The vast majority of medical treatments are performed to reduce existing symptoms of illness and prevent their recurrence. This occurs when the individual becomes ill and seeks medical assistance. The homeopathic treatment would normally be expected to be administered after the onset of the illness. In Schulz's work and the overwhelming number of examples of hormesis in the published literature, the investigations did not involve exposures after the onset of disease or chemically induced injury. Even though Schulz believed that his findings were at the core of homeopathic understanding, the scientific community made a critical error in not challenging his interpretation. However, instead it challenged the reliability of Schulz's findings and his dose-response generalization, a decision that would prove to have far-reaching implications for pharmacology and toxicology. Given this strategic, although incorrect decision on how to challenge Schulz, two courses of action emerged: (1) the Schulz biphasic dose-response model (called the

Arndt–Schulz law at the time) had to be marginalized, and (2) a credible alternative had to be formulated, and this becoming the threshold dose-response model, the model on which 20th century clinical pharmacology, toxicology, and risk assessment would be based.

The most notable critic of Schulz was Alfred J. Clark (1885–1941), a highly accomplished pharmacology researcher and scholar, who had considerable influence among academics and government regulators (Verney and Barcroft, 1941; Gaddum, 1962). Nearly 70 years after his death, Clark remains a highly respected figure in pharmacology, with graduate fellowships and a distinguished chair in pharmacology at Edinburgh named in his honor. Clark (Clark, 1933, 1937) was the author of several highly influential, multiedition textbooks that criticized Schulz and his dose-response theories in highly dismissive ways (Calabrese, 2005a) while also linking him with the “extremist” elements within homeopathy (Clark, 1927). In fact, Clark’s *Handbook of Pharmacology* was highly regarded, being published as late as 1970, nearly three decades after his death, and influenced several generations of pharmacologists and toxicologists.

Clark’s professional successes were due in considerable measure to his careful and objective evaluation of data and his capacity to obtain and integrate massive amounts of complex and technical information in scientifically valid and insightful ways. In the case of his analysis of Schulz, such thoroughness and objectivity were surprisingly below his normally high standards, with a retrospective evaluation (Calabrese, 2005a) revealing that Clark was very selective in his use of the published literature to support his position while failing to report substantial independent findings that supported Schulz’s work with yeast and disinfectants (Branham, 1929), as well as his general biphasic dose-response concept (Calabrese and Baldwin, 2000a, Calabrese and Baldwin, 2000b, Calabrese and Baldwin, 2000c, Calabrese and Baldwin, 2000d, Calabrese and Baldwin, 2000e). Of particular note is that Schulz was not in a position to defend himself, given that Clark’s criticisms intensified after Schulz entered retirement in the early 1920s, and Schulz died (1932) before the first editions of Clark’s two critical books (Clark, 1933, 1937). Furthermore, when the prominent surgical and biomedical researcher August Bier came to his defense, political forces were quickly mobilized to strongly criticize the once-esteemed Bier (Goerig et al., 2000), who had been nominated for the Nobel Prize in Biology and Medicine on multiple occasions, sending a not-so-subtle message to other scientists, even those of considerable achievement and reputation, who might similarly wander from the “party line.”

Clark’s criticism of homeopathy and Schulz occurred at a time when homeopathic medicine was severely criticized by the so-called Flexner report (Flexner, 1910), which, together with the ongoing efforts by its author, with the backing of the Rockefeller Foundation, over the next two decades effectively led to the closing of the vast majority of homeopathic medical schools in the United States (Berliner, 1985). The final intellectual component of the tipping point regarding the dose-response concept occurred when colleagues of Clark’s (Gaddum, 1933; Bliss, 1935) (note that Clark’s assistance was acknowledged in the Bliss paper) independently

derived the probit dose-response model to account for responses above the so-called toxicology/pharmacology threshold. A critical statistical refinement offered by the esteemed biostatistician R. A. Fischer in an appendix of the Bliss (Bliss, 1935) paper utilized the maximum likelihood estimate to constrain responses to asymptotically approach control-group values in the low-dose zone. In effect, any response below the control group was to be judged as variation, thereby denying the possible biological reality of the J-shaped or inverted-U-shaped dose-response curve. Multiple forces therefore converged and were to control how toxicology and pharmacology considered the dose-response relationship for the next 80 years. Acceptance of the threshold dose-response model would drive the development of these fields, including the selection of animal models, study designs, and risk assessment practices and government regulation.

The exclusion of the hormetic-like dose-response relationship from the mainstream of pharmacology and toxicology during the 20th century was strikingly successful even though there were a substantial number of high-quality research papers supporting the hormetic perspective (Calabrese and Baldwin, 2000a, Calabrese and Baldwin, 2000b). Despite such supportive scientific studies, the hormetic dose-response relationship became marginalized as traditional medicine established its control and directions on the field, transforming the discipline of toxicology in the process. By essentially denying the existence of the biphasic dose-response relationship (Calabrese and Baldwin, 2000c, Calabrese and Baldwin, 2000d, Calabrese and Baldwin, 2000e), 20th century scientific leaders molded toxicology into a high-dose, few-doses discipline. A consideration of the historical development of the reliance of the U.S. National Cancer Institute's (NCI) cancer bioassays on only two doses—the maximum tolerated dose (MTD) and MTD/2—to define the toxicity spectrum illustrates the impact of Clark's dictum on 20th century chronic toxicity and carcinogen evaluations. By truncating the focus of toxicology to above-threshold responses, what did the field miss? Before that question can be answered, it is necessary to establish that biphasic dose responses exist and are reproducible and to discuss their mechanistic foundations and frequency.

## **The Hormetic Dose-Response Relationship**

An important factor in the evaluation of hormetic-like biphasic dose responses is that numerous investigators have reported observations supportive of this dose-response relationship in highly diverse biomedical fields with a notably increased frequency from the mid 1970s and early 1980s to the present. These observations have been associated with various types of technological improvements, including the markedly enhanced capacity to measure lower and lower concentrations of chemicals in various media, thereby permitting toxicological and pharmacological evaluations over a far greater dose range than previously envisioned. It also has been related to major developments in the area of cell culture, including the use of 96-well and higher plates, which permit the assessment of large numbers of chemicals over a broader range of concentrations in a highly cost-effective manner. These

advances have been particularly evident in the evaluation of chemically induced immune responses (Calabrese, 2005b), as well as in the assessment of the responses of human tumor cell lines to a wide range of endogenous and exogenous agents (Calabrese, 2005c).

Even though hormetic-like biphasic dose responses have been widely and increasingly reported, it has been common for various biological subdisciplines to use unique descriptors/terms for biphasic dose-response relationships, often specific to each discipline (Table 1). Table 2 provides a historical time line of the citations of some of the main terms used to describe hormetic-like biphasic dose responses based on the Web of Science database. This table documents that the biphasic dose-response concept has shown an increase in citation frequency over the last several decades, that is, long after the dose-response concept had been firmly established and administratively “fixed” within the fields of pharmacology and toxicology and its governmental regulatory agency analogues such as the U.S. Food and Drug Administration, the U.S. Public Health Service, and, since 1970, the U.S. Environmental Protection Agency.

**Table 1** Terms Used to Describe Biphasic Dose Responses

U-shaped	Inverted U-shaped
J-shaped	Bidirectional
Biphasic	Hormesis
Dual effects	Arndt–Schulz law
Bimodal	Hueppe’s rule
Bitonic	Bell-shaped curve
Pharmacological inversion	Yerkes–Dodson law
Paradoxical effect	Functional antagonism

**Table 2** Frequency of Citation by 10-Year Period in Web of Science of Terms That Could Describe Hormesis and Related Terms: 1945–2007

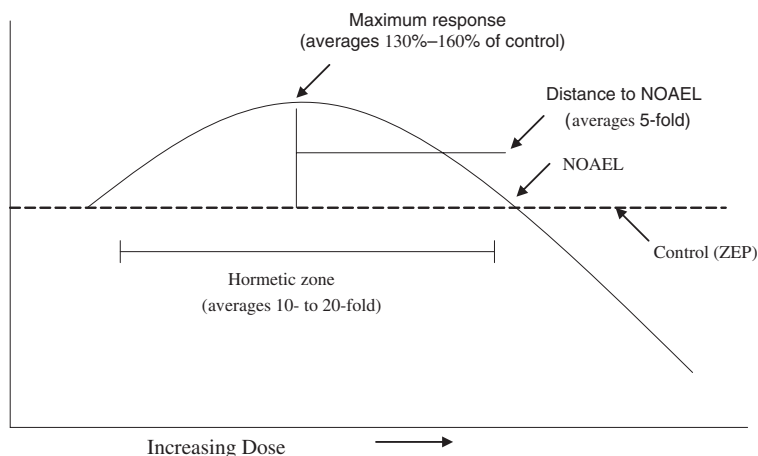
Term	Frequency of citation						
	1945–1954	1955–1964	1965–1974	1975–1984	1985–1994	1995–2004	2005–2007
Bell-shaped curve	0	0	0	1	193	495	128
Bell-shaped dose-response	0	0	0	2	97	252	38
U-shaped dose-response	0	0	0	0	48	195	58
U-shaped curve	0	0	0	1	149	408	145
J-shaped curve	0	0	0	0	21	114	39
Biphasic dose-response	0	0	1	9	182	346	63
Functional antagonism	0	2	0	23	341	1,235	330
Hormesis	1	1	0	10	92	485	247

These terms have been used to describe dose responses with essentially similar quantitative features and general mechanistic strategies. This broad set of descriptor terms for what is believed to be the same general dose-response phenomenon has created a significant challenge to the broader biological/biomedical field because this terminological diversity can adversely affect the capacity to discern the general nature of the hormetic-like biphasic dose-response relationship (Calabrese et al., 2007).

## The Hormesis Database

To assess hormetic dose responses more systematically and objectively, a database was created in which dose responses had to satisfy rigorous *a priori* evaluative criteria based on study design, statistical significance, magnitude of the stimulatory response, and reproducibility of findings. Information from this database is now extensive, with more than 8,000 dose responses with evidence of hormesis. Analyses of the database have been used to assess the quantitative features of the hormetic dose-response relationship and their capacity for generalization across biological model, endpoint, and chemical class/physical stressor (Calabrese and Baldwin, 1997; Calabrese and Blain, 2005).

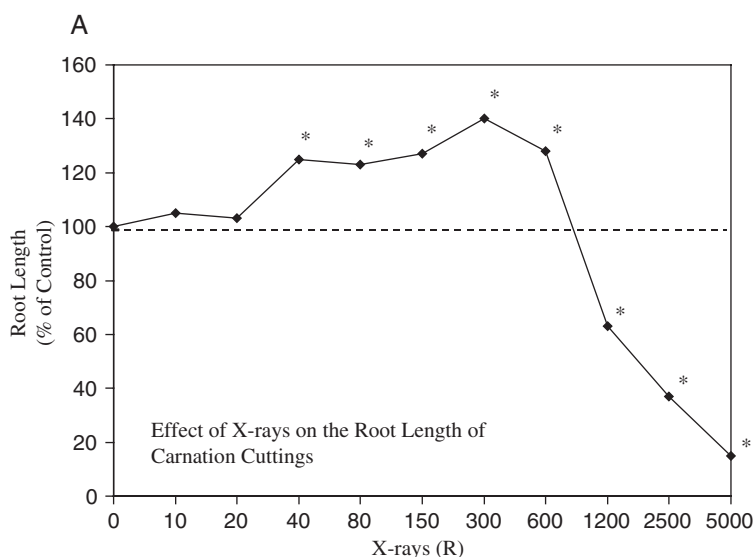
The hormetic dose-response relationship is similar to the threshold dose-response relationship for responses that exceed the toxicological/pharmacological threshold. However, it is below this threshold where the two dose-response models differ. In the case of the threshold dose-response model, there is the assumption that there is no significant treatment-related effect below the threshold, with responses predicted to randomly bounce above and below the control-group value. With respect



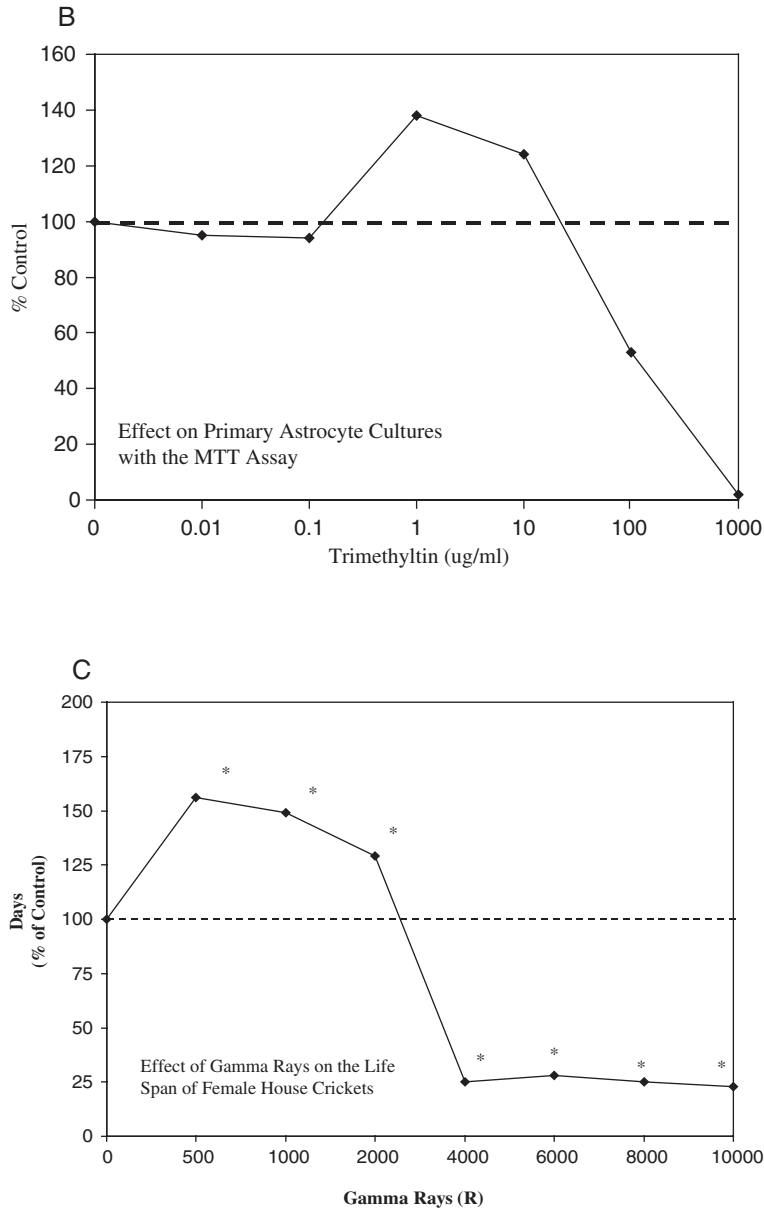
**Fig. 1** Dose-response curve showing the quantitative features of hormesis. NOAEL, no observed adverse effect level; ZEP, zero equivalent point (ZEP) (i.e., value equal to the control value)



to the hormetic dose-response model, there is the expectation that responses will nonrandomly increase above that of the control group starting immediately below the threshold response. Analysis of data from the hormesis database (Calabrese and Blain, 2005) indicates that the magnitude of the stimulatory response is characteristically modest, almost always less than twice that of the control group, with the strong majority of maximum stimulatory responses being within the range of 30% to 60% greater than control values (Fig. 1). The width of the stimulatory response is generally within a range extending from immediately below the threshold to about 1/20 of the threshold value. However, the stimulatory range may vary appreciably, with about 2% of dose responses in the hormetic database having a stimulatory width of greater than 1,000-fold. Figure 2 displays a broad range of examples of hormetic dose-response relationships. These examples illustrate that hormetic



**Fig. 2** Selected examples of hormesis, reflecting a broad range of biological models, endpoints, and chemicals/physical stressor agents. **A.** Effect of X-rays on the root length of carnation cuttings (Bors and Zimmer, 1970). **B.** Effect on primary astrocyte cultures with the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay] (Cookson et al., 1995). **C.** Effect of gamma rays on the lifespan of female house crickets. (Hunter and Krithayakiern, 1971). **D.** Effect of acridine on reproductive performance in *Daphnia* (Parkhurst et al., 1981). **E.** Effect of lead and copper on the survival of springtails (Sandifer and Hopkin, 1997). **F.** Effect of dexamethasone on cell growth and viability of cultured human retinal pigment epithelial (RPE) cells (Wu et al., 2002). **G.** 2-Methyl-4-chlorophenoxyacetic acid (MCPA) and oat shoot growth (Wiedman and Appleby, 1972). **H.** Cadmium and aquatic plant nitrate reductase activity (Rai et al., 1998). **I.** Aluminum and mouse blood gamma-aminolevulinic acid activity (Vieira et al., 2000). **J.** Alcohol and rat serum levels (Cicero and Badger, 1977). **K.** Cyclopentyladenosine (CPA) and porcine coronary artery (Merkel et al., 1992). **L.** Arsenic and human lymphocyte DNA synthesis (Meng 1993). **M.** Effect of streptomycin on mortality in mice (Welch et al., 1946). **N.** Modulation of fibroblast proliferation of oxygen free radicals (Murrell et al., 1990)



**Fig. 2** (continued)

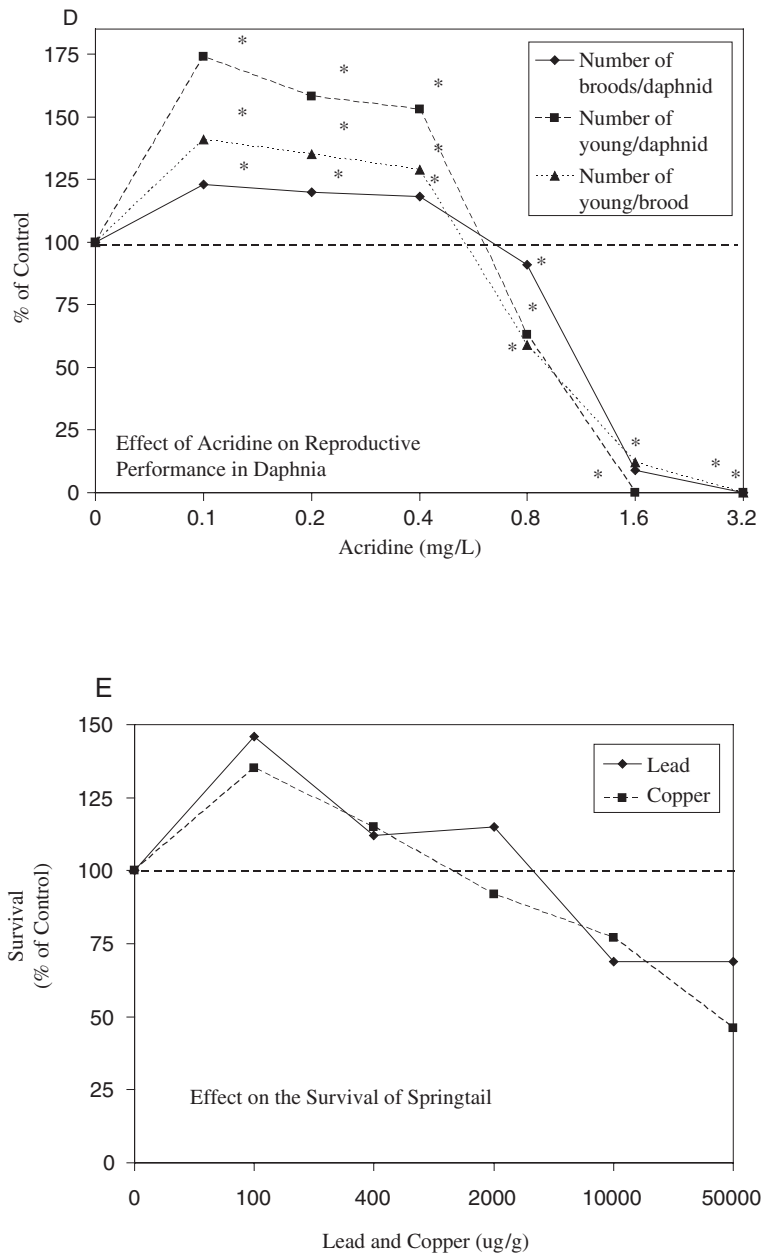
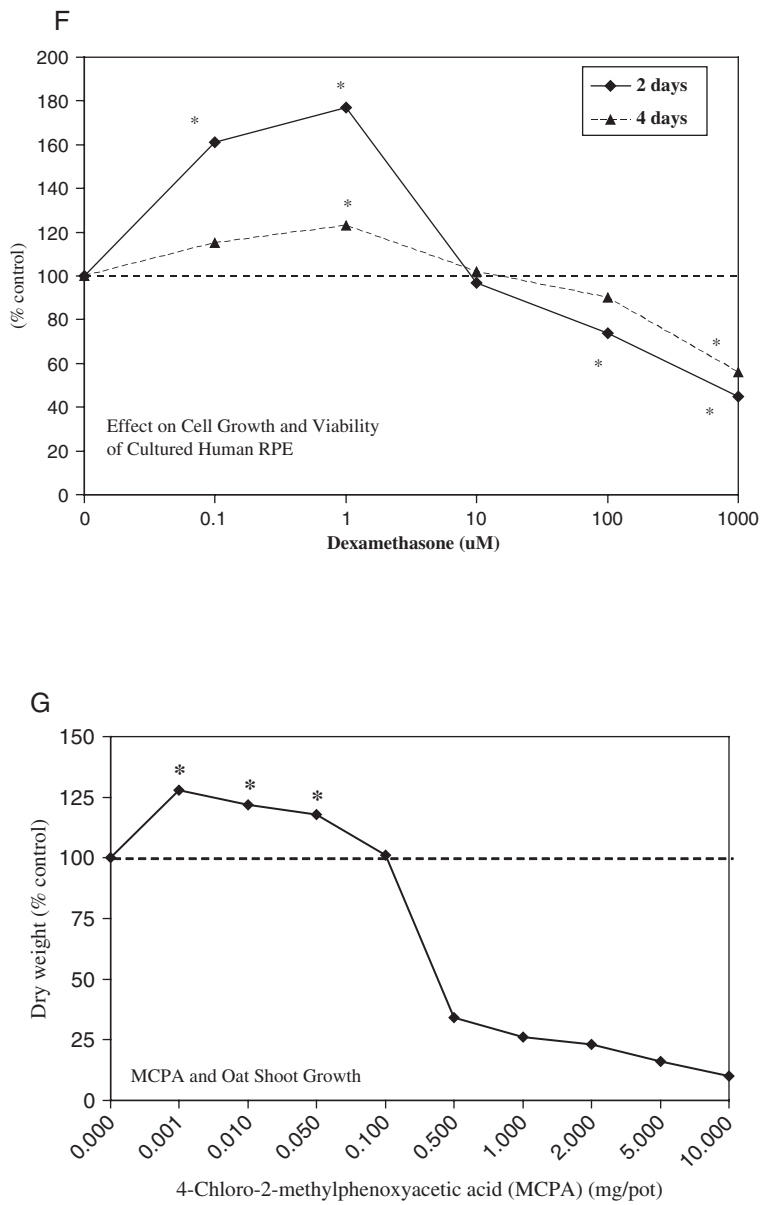


Fig. 2 (continued)



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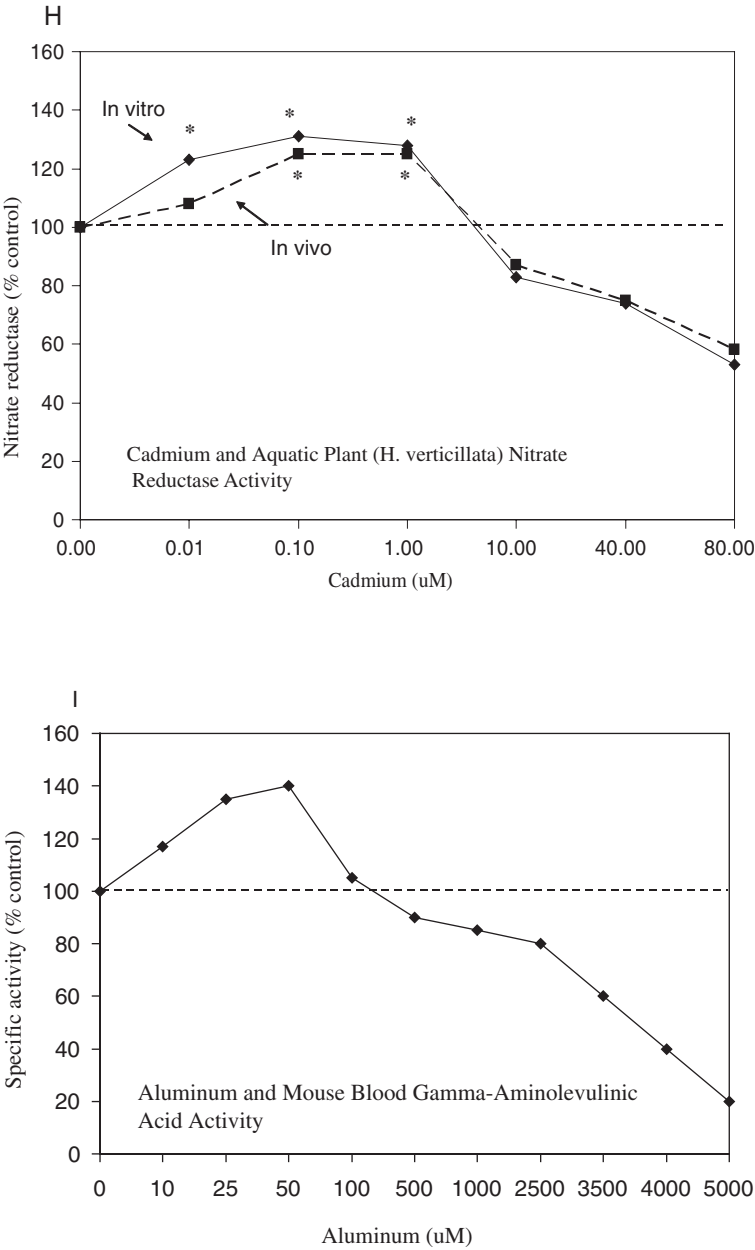


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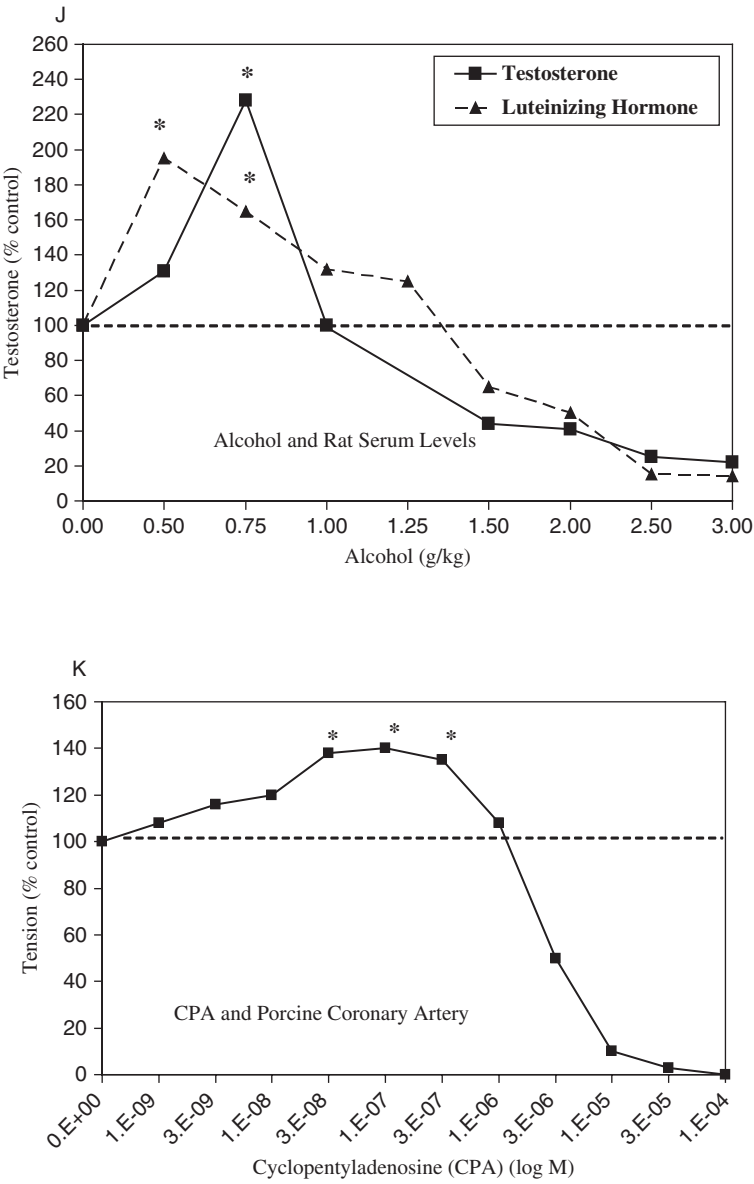


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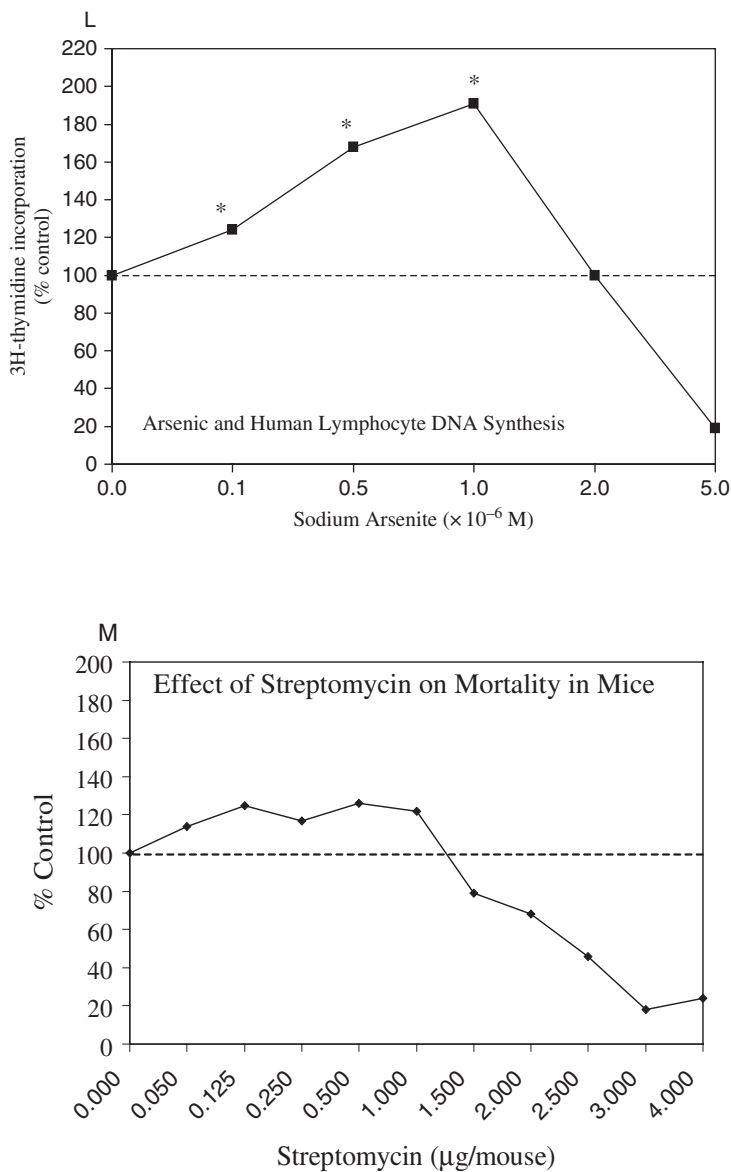
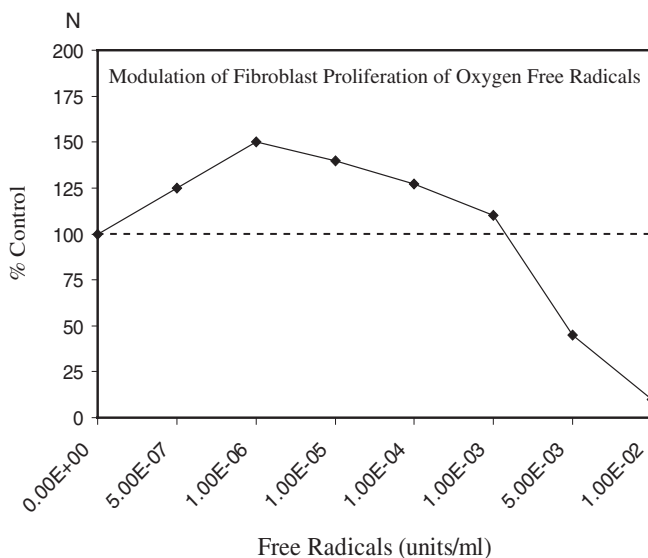


Fig. 2 (continued)



**Fig. 2** (continued)

effects occur across a wide range of biological models, endpoints, and chemical classes. Detailed assessment of the hormetic database indicates that the hormetic dose-response relationship is both highly generalizable and conserved within an evolutionary framework.

## The Frequency of Hormesis in Toxicology and Pharmacology

A second hormetic database was created to assess a limitation in the aforementioned database. That is, its lack of a priori entry criteria prevented the capacity to estimate the frequency of hormesis in the toxicological and pharmacological literature. Even though there was considerable evidence demonstrating the occurrence of hormetic dose-response relationships and their biological and statistical features, the database could not address the question of whether hormetic responses would be expected to occur in 1% or 50% of the cases of properly designed experiments. This is important, especially for regulatory agencies that may have different priorities for responses with a low frequency than for those that are common and highly generalizable. Such determinations may affect strategies for how regulatory agencies manage such chemicals within a standard setting framework. If hormetic effects are of low frequency (e.g., occur in less than 1% of studies), they may be treated on a case-by-case basis. If they occur with fairly high frequency, then general procedures would likely be developed for their systemic evaluation. In the case of the second hormetic database, approximately



21,000 articles were assessed for their capacity to satisfy initial a priori entry criteria; those satisfying such criteria were then subjected to a priori evaluative criteria. This assessment revealed that hormetic effects occurred in nearly 40% of the cases that satisfied both the entry and evaluative criteria (Calabrese and Baldwin, 2001). These findings provided the first general frequency estimate of hormetic dose responses in the toxicological and pharmacological literature. This database was used subsequently to test the capacity of the hormetic and threshold dose-response models to predict responses below toxicological/pharmacological thresholds. In this specific assessment, hormetic dose responses occurred far more commonly (i.e., 2.5:1) than the threshold dose-response model predicted (Calabrese and Baldwin, 2003a). These hormetic findings were extended via the use of a U.S. NCI database on the effects of nearly 2,200 potential antitumor drugs on 13 strains of yeast (i.e., 57,000 concentration responses) with well-characterized genetic alterations relating to DNA repair and cell cycle control (Calabrese et al., 2006). These findings add strong support to the hypothesis that reproducible stimulatory responses occur below traditional toxicological/pharmacological thresholds and that these responses, although quite common, are poorly predicted by the threshold model, whereas the hormetic model predicts such responses with considerable accuracy.

Comprehensive assessments of hormetic responses have been published in the areas of immunology (Calabrese, 2005b), human tumor cell lines (Calabrese, 2005c), and neuroscience, including neuroprotection (Calabrese, 2008a), neurite outgrowths (Calabrese, 2008b), memory (Calabrese, 2008c), pain (Calabrese, 2008d), stress responses (Calabrese, 2008e), anxiolytic drugs (Calabrese, 2008f), antiseizure medications (Calabrese, 2008g), and stroke (Calabrese, 2008 h), and detailed critical assessments are available in other areas as well, including chemotherapeutics (Calabrese, 2003a), apoptosis (Calabrese, 2001a), cellular migration behavior (Calabrese, 2001b), environmental contaminants (i.e., inorganics) (Calabrese, 2003b), and numerous endogenous agonists, including dopamine (Calabrese, 2001c), nitric oxide (Calabrese, 2001d), estrogen (Calabrese, 2001e), testosterone (Calabrese, 2001f), serotonin (Calabrese, 2001g), opioids (Calabrese, 2001h), and adrenergic agents (Calabrese, 2001i). This substantial body of literature indicates that hormesis is highly generalizable, being independent of biological model, endpoint, and stressor. These findings indicate that the threshold models and models that are linear at low doses often fail to accurately predict low-dose responses.

## Implications of Hormesis

Detailed evaluations of the hormetic database indicate that the hormesis concept may have significant impacts on multiple areas, including biological concepts, toxicological/pharmacological principles, environmental risk assessment theory and practices, clinical medicine, and agricultural/industrial applications. These are now discussed.

## ***Impact on Biological Concepts***

### **Hormesis Measures Performance**

The low-dose stimulation as observed in toxicologically based hormetic dose-response relationships reflects *biological performance*, whereas inhibitory responses occurring at higher doses typically describe toxicity. This general scheme is also the case within a pharmacological framework in which a similar stimulatory response occurs typically at doses below the threshold, whereas either inhibition or a return toward control values occurs as the dose increases due to toxicity, receptor desensitization, or other factors.

Toxicology has long been dominated by an emphasis on very high doses and the assessment of toxic responses. In the case of toxicity, there is an expansive potential for an increase in the expression of injury as the dose increases beyond the threshold. This may be seen in the release of tissue enzymes into the serum as in the case of biomarkers of liver damage or the number of tumors per animal in cancer bioassays. The potential for the system to display biological performance as seen with the hormetic dose response has been routinely missed because below-threshold responses have not been systematically studied. Recognizing that the hormetic stimulatory response is a manifestation of biological performance is a novel conceptual interpretation. Biological performance responses occur at all levels of biological organization, conform to the constraints of biological plasticity, and optimize system function. There are numerous endpoints that express biological performance, including cell proliferation, growth, longevity, strength, disease resistance, increases in cognition, and others. Thus, the hormetic dose response expands the dose-response concept, with the expectation that there is both an above-threshold toxicity feature and a below-toxicity, stimulatory component that describes biological performance.

There are conditions when the low-dose performance stimulation may not be beneficial to the individual. This may occur in the case of enhanced cellular proliferation causing organ enlargement such as the prostate (Chueh et al., 2001), enhanced risk of a detached retina via retinal epithelial cell proliferation (Wu et al., 2002), or the proliferation of harmful microorganisms (Randall et al., 1947; Garrod, 1951). Nonetheless, the concept of hormesis as an expression of biological performance in these cases remains valid, even if it occurs in an infectivity circumstance or when a tissue can be biologically “tricked” into a response that may be harmful to the organism. The performance response remains one that is of limited magnitude, is constrained by plasticity, and optimizes a response function.

### **Hormesis Provides Quantitative Estimates of Biological Plasticity**

Because the performance function is highly generalizable, with consistent quantitative features, the hormetic dose response may represent a general estimate of the magnitude of biological plasticity across biological systems and possibly account for the marked constraints in the magnitude of hormetic stimulatory effects. If this

were the case, it would represent a significant unifying biological concept. It suggests that the low-dose performance stimulation, that is, the hormetic stimulatory response, may provide the quantification of one major type of biological plasticity.

### **Adaptive Response/Preconditioning: Manifestations of Hormesis**

Over the last several decades there has been considerable research on the adaptive response in radiation and chemical toxicology. The adaptive response occurs when a prior low dose of a toxic agent or stress condition enhances the capacity of the affected cell, organ, or organism to resist the toxicity of a subsequent and more massive exposure to the same or similar agent or stress condition (Calabrese, 2008i). A similar type of adaptive response was named preconditioning after investigators observed that a hypoxic stress administered 24 hours prior to a massive myocardial infarction in dogs reduced cardiac damage by nearly 80% (Murry et al., 1986). Both the adaptive response and preconditioning concepts describe a similar temporal process in which a low prior dose of a stressor agent upregulates a cascade of molecular events that results in the temporary protection against a subsequent substantial threat. The key connection of the adaptive/preconditioning response to the hormesis concept is found in a detailed evaluation of the “adapting” or “preconditioning” doses. That is, prior dosing displays a dose-response optimum that maximizes the subsequent protective effect. Lower and higher doses display a drop-off of the protection response. Higher adapting or preconditioning doses may act to further exaggerate the toxicity of the more massive subsequent exposure. If this relationship is plotted, it represents a biphasic dose response with quantitative features that are consistent with the hormetic dose response.

The relationship of hormesis to the adaptive response was explored by Davies et al. (Davies et al., 1995), who defined the optimal condition for a transient hydrogen peroxide adaptation as measured by cell viability in the yeast model *Saccharomyces cerevisiae*. In a critical first step, the authors determined the effects of hydrogen peroxide on cell proliferation employing up to nine concentrations. A hormetic-like biphasic dose-response relationship was reported in which low hydrogen peroxide concentrations (0.4 mM or less) enhanced cell colony growth by approximately 30%. The hydrogen peroxide-induced toxicity started to occur between 0.5 and 0.8 mM. Based on these findings, an adapting or preconditioning dose was selected to be one in the low-dose stimulatory/hormetic zone. The yeast cell treatments that received the adapting dose in the hormetic zone followed by the challenging (i.e., cell killing) dose not only showed the adaptive response, but also displayed a percentage viability that exceeded the original control value by approximately 20% to 50%.

### **Hormesis as an Expression of Allometry**

A significant concept in the biological sciences is that of allometry, which provides a quantitative integration of numerous biological parameters as a function of body weight and/or surface area (Calder, 1996). Allometric relationships are particularly

important for the toxicological and pharmacological sciences because they provide a biologically based biomathematical framework for estimating the responses of drug treatments both on an interindividual basis and extrapolated across species. An important observation is that hormetic dose-response relationships can be modeled allometrically, and these relationships are consistent within and between species. The hormetic response represents a similar proportional increase to a normalized control group independent of species, thereby providing the basis for the allometric relationship. This observation strongly supports the generalizability of the hormetic dose response across species for human endpoints and integrates this concept within an evolutionary framework.

## **Toxicological/Pharmacological Implications**

### ***Factors Affecting the Recognition of Hormetic Dose-Response Relationships***

#### **Use of Multiple Terms**

Many terms have been used to describe the hormetic dose-response relationship (Table 1). The use of such a wide range of terms, many specific to biological sub-disciplines, for the same quantitative features of the dose-response relationship has created conceptual confusion on the nature of the relationship in the low-dose zone. One significant contributory factor to the use of such a wide range of terms for the same apparent dose-response concept is the progressive specialization within the sciences, which reduces communication between specialties.

#### **Modest Stimulation and Historically Weak Study Designs**

Further contributing to the difficulty in recognizing the occurrence, generalizability, and reproducibility of the hormetic-like biphasic dose-response relationship is that most hormetic dose-response relationships are characterized by a modest stimulation (30% to 60%) in the below-threshold zone, a feature that is its most distinguishing characteristic (Calabrese and Blain, 2005). Given the modest magnitude of the hormetic stimulatory response, it can be difficult to verify when studies have only few doses that are intended to document toxicity and estimate the toxic threshold.

#### **Control Group: High Variation**

The use of biological models with high background variability is problematic in the evaluation of hormetic hypotheses. The presence of such variability places heightened demands on sample size to increase statistical power to evaluate possible treatment effects.

### **Low Background Disease Incidence**

The field of toxicology adopted the use of biological models with very low disease incidence to maximize statistical power while using as few subjects as possible to reduce financial expenses associated with the conduct of experiments. This set of study design challenges still exists, as evidenced in the standard testing protocols required by most governmental regulatory agencies. When a control group displays a very low background disease incidence, it is essentially impossible, at least in a practical sense, to assess hormetic dose-response hypotheses. This testing strategy, which has historically governed hazard assessment, indicates that hazard assessment goals and practices lack the capacity to assess the presence or absence of hormetic-like biphasic dose-response relationships. The use of control groups with such negligible disease incidence reinforces the belief that the threshold dose-response model is valid and appropriate for extrapolation in the low-dose zone, an assumption that has been discredited (Calabrese and Baldwin, 2003a; Calabrese and Baldwin, 2001; Calabrese et al., 2006).

### **Lack of Temporal Component**

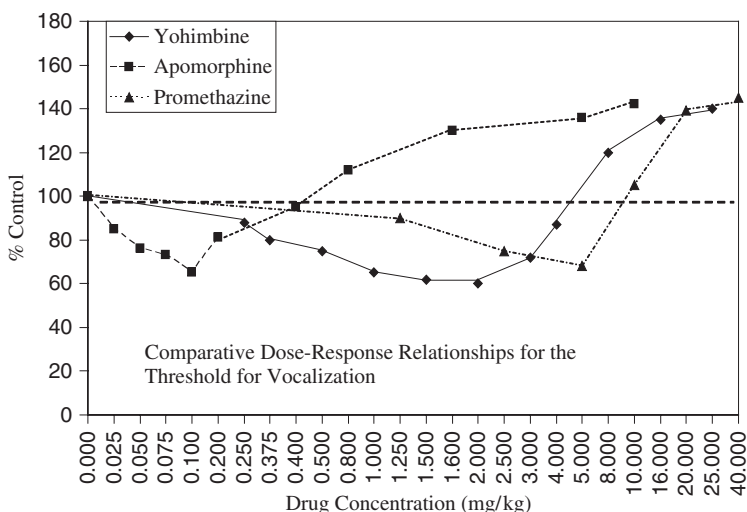
Hormetic dose responses may be difficult to discern because they often require a time component that is typically lacking in standard hazard assessments. Because hormetic dose responses represent a modest overcompensation stimulation following a disruption in homeostasis (i.e., toxicity), it is necessary to document the biological responsiveness over time to assess the effects of the chemical or physical stressor. The hormetic dose response can therefore be easily missed if the biological model is not tested over the proper range of doses and within the appropriate temporal framework.

### **Summary**

In the chronic bioassays required by regulatory agencies, there is little to no opportunity to assess hormetic effects because they use too few doses, very high doses, and animal models with low background disease incidence. Failure to consider the possibility of a hormetic dose-response relationship has significant implications, preventing the identification of possible harmful or beneficial effects in the below-threshold zone.

### ***Chemical Potency and Hormesis***

Pharmaceutical agents that affect the same endpoint may often display profoundly different potencies. However, despite the fact that an agent may be far more potent than another agent for the same endpoint, the quantitative features of the hormetic response are remarkably similar (Calabrese, 2008d) (Fig. 3). As suggested earlier,



**Fig. 3** The J-shaped dose-response relationships for yohimbine, apomorphine, and promethazine for pain. Comparison of Figs. 1, 2, and 4 of Paalzow and Paalzow (1983a), Paalzow and Paalzow (1983b), and Paalzow and Paalzow (1985), respectively

stimulatory responses are similarly limited by the constraints imposed on biological systems by their inherent plasticity. Potency therefore does not affect the quantitative features of the hormetic dose response.

### *Hormesis: A Novel Concept of Synergy/Potentiation*

There is considerable research on chemical interactions concerning toxicity, that is, the above-threshold side of the dose-response relationship (Calabrese, 1991). Regulatory agencies have written policy statements for how to assess interactions that are additive or synergistic (U.S. EPA, 1986). However, they have not addressed the issue of chemical interactions on the performance side of the dose-response relationship (i.e., below the threshold) (Calabrese, 2008j). The distinction between the toxicity and the performance parts of the dose-response relationship with respect to chemical interactions also has not been considered in the assessment of the effects of pharmaceuticals on human health. In the case of chemical interactions and hormesis/performance, the dose response in the low-dose stimulatory zone is constrained by the limits imposed by biological plasticity. Increases in response would not be expected to exceed the modest stimulation of only 30% to 60% rather than the multifold possible increases seen in the toxicity side of the dose response relationship. In a practical sense, hormesis-related synergy would be observed as the reduction in dose needed to achieve a near-maximum response that would be constrained by plasticity. This was reported by Flood et al. (Flood et al., 1983, 1985), who assessed the

effects of drugs on cognition in rodent models. They combined exposures of agents that could individually maximally enhance cognition by about 50%. When these drugs were combined in various ways, the maximum response was not increased, but the amount of agent needed to achieve the maximum, although modest, response was profoundly reduced for each of the agents used in the drug combination experiments. Thus, synergy in these performance-oriented experiments was most clearly observed at the level of dose rather than at the level of response. A practical implication of these findings is that even though the absolute degree of cognition was not enhanced in drug combinational studies beyond what was achieved with a singly acting agent, the modest maximum response could be achieved by using far lower quantities of the several combined drugs, thereby markedly reducing the likelihood of undesirable drug side effects.

Even though the chemical interaction concept was observed best on the dose side in the assessment of hormesis/performance, it could also be seen on the response magnitude side. However, any response synergy would be difficult to observe because it would have to occur within the 30% to 60% maximum response range. This suggests that response-side examples of synergy within a hormetic setting can be addressed only within experimental settings in which the control group has very low background variability.

The implications of the constraints of biological plasticity on chemical interactions are important for the pharmaceutical industry. Drug treatments, whether administered singly or in combination, are not likely to achieve a response greater than the hormetic maximum. Thus, if a drug increases memory by 30% to 60% in an Alzheimer's disease patient, it should not be expected that a drug combination would exceed this value.

### ***Interindividual Variation and Hormesis***

The hormetic/performance stimulatory response begins immediately below the toxic threshold. There is often less than a factor of 5 to 10 between the optimal dose for performance and the onset and occurrence of toxicity. Because humans often display a range of interindividual variation between 10- and 20-fold and sometimes even greater (Calabrese, 1985), estimated "optimal" doses of drugs for the so-called average person are likely to display a range of possible responses in a heterogeneous population, including being highly effective, that is, achieving the optimal zone, but also exposures at which the dose misses the optimal zone on either the low or high side, resulting in little or no treatment effect or possible toxicity, respectively. The overlapping of optimal performance and toxicity zones due to patterns of interindividual variation in response is common in clinical practice. This requires continual fine-tuning to optimize the patient treatment dose. It would be far less challenging for the clinician if the goal were to kill harmful microbes or tumor cells. In this case, the physician would be directing attention to the toxicity side of the threshold response. This phenomenon also has important implications for the interpretation of epidemiological studies, as discussed next.

## ***Epidemiology and Hormesis***

Dose-response relationships may be markedly affected by the degree of heterogeneity within the population. This would be a particular consideration for epidemiological investigations in which there is considerable ethnic, age, and health variability. To assess the influence of heterogeneity on the overall integrated population-based dose-response relationship, we conducted a series of simulations in which a number of subgroups were identified and given a specific dose-response relationship characteristic that could be hormetic, threshold, or linearity, and we took differential proportions of the total population. This exercise demonstrated that by altering any of the foregoing parameters, one could significantly change the overall shape of the population-based dose-response relationship. The final integrated population-based shape of the dose-response relationship could be readily made to become linear, threshold, biphasic, or multiphasic.

This exercise indicated that epidemiological evaluations could be problematic in the assessment of a hormetic or any other type of dose-response relationship. The occurrence of the intergroup dose-response variability and its differential proportion within the population may create a blended dose-response relationship that could mask the dose-response dynamic that occurs at each subgroup level. Recognition of this possible complexity in assessing the nature of the dose response, especially in the low-dose zone, is an important consideration affecting data interpretation.

## ***Hormesis and Medicine***

Hormesis has profound implications for the field of medicine because it defines the qualitative and quantitative features of the dose response. We now briefly describe a broad spectrum of medical applications.

### **Low-Dose Stimulation of Tumor Cells**

The hormetic dose-response relationship predicts that antitumor agents may enhance the proliferation of tumor cells in the low-dose zone. This prediction was confirmed in an extensive review of the effects of antitumor agents on the proliferation of human tumor cell lines (Calabrese, 2005c). Hormetic-like biphasic dose responses were reported in 136 human tumor cell lines from more than 30 tissue types for more than 120 agents. Although the mechanisms were often different, being specific for each tumor type, the shape of the dose-response relationships is consistent with the hormetic biphasic model. Even though the endpoint measurement for response varied from 1 hour to 21 days, depending on the agent and the tumor cell line, a hormetic biphasic dose-response relationship was consistently reported.

These findings suggest that many antitumor agents have the potential to enhance tumor cell proliferation in patients. This situation would be of particular concern for agents with long biological half-lives. For example, the chemotherapeutic antitumor agent suramin has a human half-life between 30 and 40 days and has the capacity to



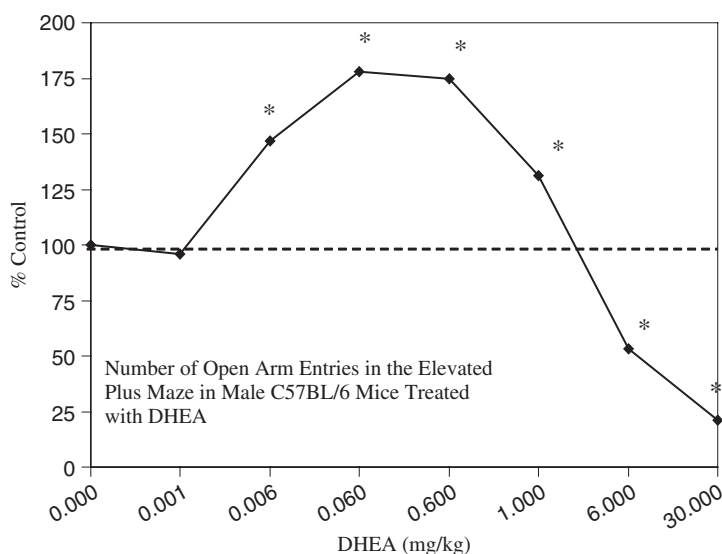
induce tumor cell proliferation in a biphasic dose-response fashion (Foekens et al., 1992).

### Low-Dose Stimulation of Microbes by Antibiotics

Similar hormetic-like biphasic dose responses have been reported for a wide range of chemicals on colony growths of bacteria, fungi, yeasts, and algae (Calabrese and Baldwin, 2000a). Similar findings were reported with synthetic antibiotics soon after their discovery in the early to mid 1940s using *in vitro* (Garrod 1951; Miller et al., 1945; Ungar and Muggleton, 1946) and *in vivo* studies (Randall et al., 1947; Welch et al., 1946) (Fig. 2m). In addition, Foley and Winter (Foley and Winter, 1949) reported that penicillin increased the mortality of chick embryos inoculated with *Candida albicans*. The possibility that low concentrations of antibiotics may have contributed to reports of enhanced patient morbidity and mortality was raised in various reports (Garrod, 1951). It is well known that various antiviral drugs can facilitate the proliferation of a broad range of viruses (Lee et al., 1999; Nyberg et al., 2004). However, the clinical implications of these findings remain to be explored.

### Anxiolytic Drugs

The hormetic dose response describes the dose-response features of anxiolytic agents regardless of which receptor pathway mediates the response. In the strong majority of cases, low doses reduce anxiety in animal models, whereas higher doses increase anxiety (Calabrese, 2008f; Melchior and Ritzmann, 1994) (Fig. 4). Such

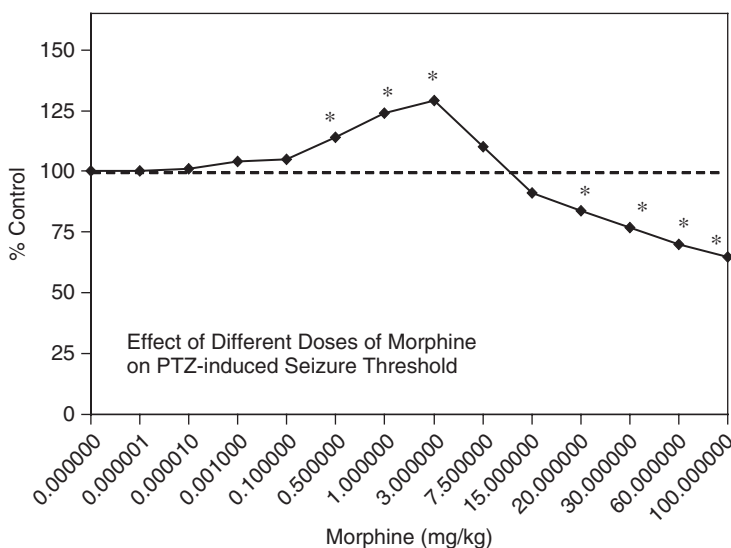


**Fig. 4** Number of open arm entries in the elevated plus maze in male C57BL/6 mice treated with dehydroepiandrosterone (DHEA). \*Significantly different from controls at  $P < 0.05$  (Melchior and Ritzmann, 1994)

findings are also consistent across the wide range of experimental behavioral protocols (e.g., elevated plus maze, social interaction test, open-field test, light-dark test, hole board test) that are routinely used to assess anxiolytic drugs.

### Antiseizure Drugs

Low doses of antiseizure drugs typically increase the threshold for the initiation of seizure responses, whereas at higher doses the onset of seizures is facilitated as the threshold for response is decreased. In screening studies for possible antiseizure drugs, animal models are routinely administered standard seizure-inducing agents, such as pentylenetetrazol (PTZ), that cause a reliable seizure response at specific doses, depending on the animal model. Possible antiseizure drugs are those that demonstrate the capacity to increase the threshold for the induction of seizures by agents such as PTZ, that is, make it more difficult for a seizure to occur. An example of this hormetic phenomenon was reported (Honar et al., 2004) with respect to morphine (Fig. 5).



**Fig. 5** Effect of different doses of morphine on pentylenetetrazol (PTZ)-induced seizure threshold. \*Significantly different from controls at  $P < 0.05$  (Honar et al., 2004)

### Memory-Enhancing Drugs

Numerous drugs have shown a capacity to enhance learning and memory in animal models, starting with the seminal work of McGaugh and Petrinovich (McGaugh and Petrinovich, 1965) with the anticholinesterase agent physostigmine. In general, such memory-enhancing drugs exhibit a U-shaped dose-response relationship regardless of the model and the specific learning or memory endpoint considered or whether

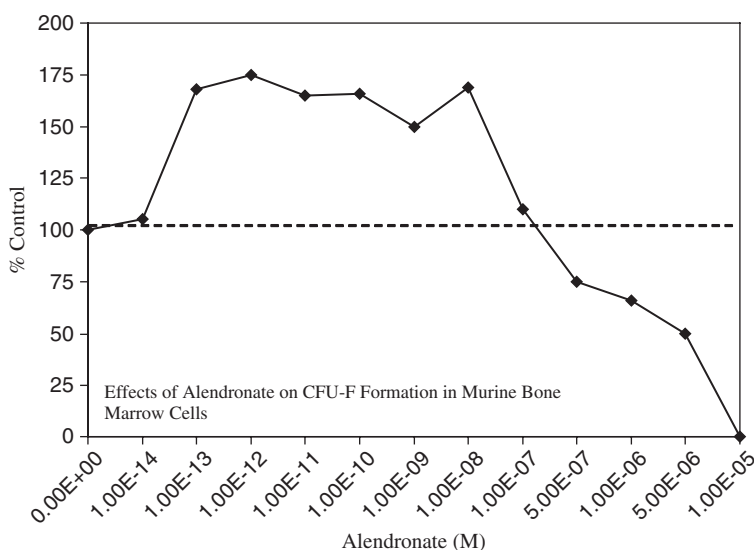
such drugs are given in combination (Flood et al., 1983, 1985). This generalized pattern of hormetic-like biphasic responses is seen with all Alzheimer's disease drugs approved by the U.S. Food and Drug Administration (FDA) (Calabrese, 2008c; Wise and Lichtman, 2007).

## Stroke Medications

Nearly three dozen possible stroke and acute brain injury medications reduce damage via hormetic mechanisms that show the standard biphasic dose-response relationship (Calabrese, 2008h). Such hormetic-like biphasic dose-response relationships have employed a diverse set of stroke and injury models, as well as agents that act via specific mechanisms and stages of the injury prevention or tissue recovery process.

## Osteoporosis

Bisphosphonates, which are widely used in the treatment of osteoporosis, follow the hormetic dose-response relationship. Detailed in vitro animal model and human investigations have demonstrated such dose responses for osteoblast formation (Giuliani et al., 1998) (Fig. 6) at drug doses that are generally equivalent to those used in the management of humans with osteoporosis (Lieberman et al., 1995; Rossini et al., 1994).



**Fig. 6** Effect of alendronate on fibroblastic colony-forming unit (CFU-F) formation in murine bone marrow cells (Giuliani et al., 1998)

## **Hair Growth**

Drugs such as minoxidil that enhances hair growth also do so in a manner that is consistent with the hormetic dose-response relationship (Boyera et al., 1997).

## **Pulmonary Hypertension**

Epidemiological investigations have associated the long-term administration of Prozac with a reduced risk of developing pulmonary hypertension in adults while increasing the risk of this disease in the fetus. Follow-up research with Sprague-Dawley rats revealed that this drug reduces the occurrence of pulmonary arterial smooth muscle cell proliferation in adult female rats in a dose-dependent manner (Fornaro et al., 2007). However, Prozac induced a hormetic-like low-dose stimulation and a high-dose inhibition for the same endpoint in the fetal rat. These findings were consistent with the protective effect seen in adult humans and the increased risk of pulmonary hypertension in the fetus. The findings were especially interesting in that a low dose induced a harmful effect, whereas the higher exposure diminished the risk of pulmonary hypertension.

## **Fibrotic Diseases (e.g., Dupuytren's Contracture)**

Pathological fibrotic conditions are associated with the presence of fibroblasts at high cell density. Many of the biochemical and ultrastructural features of fibrosis are thought to be secondary to the increase in fibroblast density. According to Murrell et al. (Murrell et al., 1990), the progression of Dupuytren's contracture, a fibrotic condition of the hand associated with microvascular ischemia, occurs by exposure to oxygen free radicals that can stimulate and inhibit the proliferation of cultured human fibroblasts in a hormetic-like biphasic manner (Fig. 2n). Prolonged stimulation in the low-dose zone may, therefore, promote the occurrence of Dupuytren's contracture, whereas agents preventing free radical release may prevent its occurrence.

## **Avoidance of Undesirable Side Effects**

In the 1990s reports began to emerge suggesting that significantly fewer side effects were observed in humans when drugs displayed characteristics of a partial agonist and a partial antagonist rather than a full agonist (Im et al., 1995; Jacobsen et al., 1996a, Jacobsen et al., 1996b; Jacobsen et al., 1999). Partial agonists/antagonists often display inverted-U-shaped dose-response relationships. The decreased risk of developing undesirable side effects from partial agonists/antagonists was hypothesized to result from a lower capacity to induce responses at nontarget tissues. The inverted-U-shaped dose-response relationship of the partial agonist/antagonist also suggested a potentially broader therapeutic

zone for drug optimization. This theoretical framework has been used by pharmaceutical companies in the search for synthetic agents with partial agonist/antagonist characteristics that display hormetic-like inverted-U-shaped dose-response relationships.

The fact that pharmaceutical companies were searching for hormetic-like inverted U-shaped dose-response relationships to minimize the undesirable side effects of drugs suggested that this solution may have been already “discovered” in the process of natural selection. Indeed, many endogenous agonists are partial agonists/antagonists with dose-response characteristics of the inverted-U-shaped type. This suggests that another reason for the selection of the hormetic dose-response relationship and its widespread generalization is to minimize the occurrence of undesirable side effects from endogenous agonists.

## ***Environmental Risk Assessment***

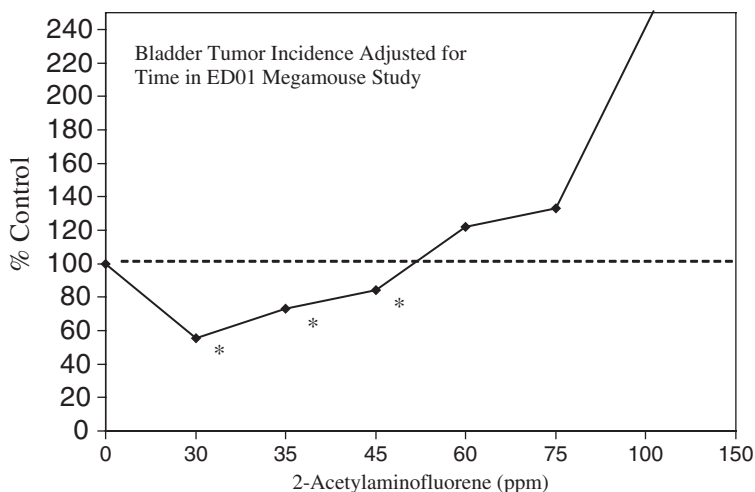
The field of risk assessment developed the concept of safety factors based on the threshold dose-response model in the 1920s. For example, in 1925 the threshold dose-response model was first employed for the protection of workers from exposure to radiation (Mutscheller, 1925). In the case of radiation, fear of cancer led in the mid 1950s to the replacement of the threshold dose-response model with a model that was linear at low doses (NCRPM, 1954). The FDA adopted the use of the threshold dose-response model along with safety factors (now called uncertainty factors) by the mid 1950s (Lehman, 1954). The threshold dose-response model continued to dominate chemical toxicology and risk assessment for all toxic endpoints until the U.S. National Academy of Sciences Safe Drinking Water Committee in 1977 recommended to the U.S. Environmental Protection Agency that they follow the lead of the radiation community and accept a linear-at-low-dose modeling approach for estimating risks from carcinogens while retaining the threshold dose-response model for noncarcinogens (NAS, 1977).

The use of linear-at-low-dose modeling for carcinogen risk assessment has been controversial principally because it can be very conservative in its estimation of cancer risks. As a result of this approach, health regulations for workers and community health have been enormously expensive as governmental agencies in the United States have tried to achieve *de minimus* risk goals such as no more than 1 excess cancer per 1 million people per 70-year lifetime. A major problem with this approach is that such model-based risk predictions cannot be practically validated experimentally or epidemiologically. In an attempt to determine the shape of the dose-response relationship of a genotoxic carcinogen (2-acetylaminofluorene [2-AAF]) in the low-dose zone, the FDA conducted what is now called the megamouse study in which 24,000 animals were used. In the end, the level of detectable risk was very insensitive, only at the level of 1 cancer per 100 people. This striking insensitivity (i.e., practical failure) of experimental systems to validate model

estimates of cancer risks at and below 1 in 1,000 created a serious potential credibility problem for regulatory agencies. It indicated that risks of 1 in 1 million that agencies often use when communicating with the public about acceptable risks is a theoretical mathematical construct that cannot be practically tested, confirmed, or rejected. Such estimates are based on an unverifiable “belief system” based on which biostatistical model is more likely to be correct in its low-dose predictions based on current understandings of biological plausibility, arguments that also are not without their own substantial degree of uncertainty.

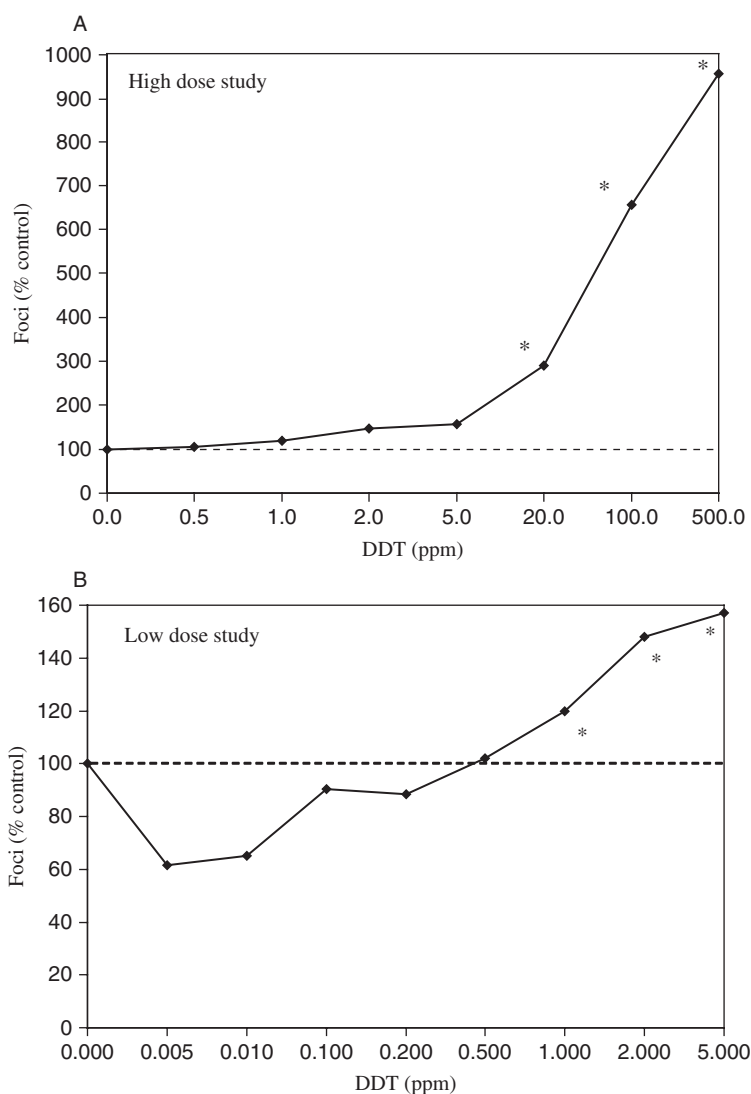
Due to the significance of the megamouse study and its potential impact on risk assessment practices in the United States and other countries, the U.S. Society of Toxicology (SOT) created a 14-member expert panel to evaluate this study’s methods and data and devoted almost an entire issue of its journal, *Fundamental and Applied Toxicology*, to its analyses (Bruce et al., 1981). Of particular importance was that the SOT expert panel concluded that this carcinogen displayed unequivocal evidence of a hormetic dose-response relationship for bladder cancer (Fig. 7). The expert panel clearly stated that not only was there a threshold for the cancerous effect, but also that below the threshold the risk notably declined below background, as predicted by the hormetic dose-response model. This J-shaped dose response was consistently seen in each of the six rooms in which the large number of animals was housed, which thereby provided a type of quasi-built-in replication. Thus, in the largest chronic rodent bioassay for cancer, the hormetic dose-response relationship was observed. This study not only supported the finding of a hormetic dose-response relationship, but also revealed that linear-at-low-dose modeling predictions could not be tested at risk levels below 1 in 100.

Similar findings of J-shaped dose responses for numerous carcinogenic and mutagenic agents also have been reported. For example, consider the case of



**Fig. 7** Bladder tumor incidence adjusted for time in the ED01 megamouse study (Bruce et al., 1981)

dichlorodiphenyltrichloroethane (DDT), the banned pesticide, which the EPA regulates as a liver carcinogen based on linear-at-low-dose modeling. Considerable research indicates that DDT is a liver carcinogen in rodents, but only at high doses. As the dose is progressively decreased, the risk of liver cancer decreases, with the dose-response relationship becoming hormetic (Fig. 8)



**Fig. 8** Effect of dichlorodiphenyltrichloroethane (DDT) on the number of placental glutathione S-transferase (GST-P)-positive foci in F344 rat livers in two bioassays assessing different but slightly overlapping doses of carcinogen. Note: As the dose decreases, the J-shaped dose-response relationship becomes evident. Also note the difference in scale between the two graphs. (Sukata et al., 2002.)

(Fukushima et al., 2005; Sukata et al., 2002). Follow-up mechanistic research has clarified the underlying mechanistic reasons for the cancerous responses at high doses and the chemoprotective effects at lower doses. As was the case with 2-AAF, the linear-at-low-dose prediction of DDT-induced hepatic foci was not validated in experimental studies, whereas the hormetic dose-response model was.

A question of considerable societal importance is whether regulatory agencies should continue to use the threshold and linear-at-low-dose models in environmental risk assessment practices, especially given that both are ineffective in predicting responses in the low-dose zone (Calabrese and Baldwin, 2001; Calabrese et al., 2006; Calabrese and Baldwin, 2003b). It is highly questionable public policy to use toxicological models for risk assessment purposes that fail to accurately predict responses in the low-dose zone. Alternatively, the hormetic dose-response model could be considered for use in risk assessment practices because it can be tested and has performed well in the same tests at which the threshold and linear models have failed (Calabrese, 2005d). The hormetic dose-response model offers a range of other advantages for use in risk assessment, as indicated in Table 3.

Although the clinical challenges of trying to determine optimal performance doses can be difficult, they are fundamentally different from those with chemical risk assessment in the environmental regulatory arena. In the case of risk assessments for noncarcinogens, the standard practice has been to use multiple independent uncertainty factors. The procedures use a factor of 10 to account for the uncertainty of extrapolating from the average response of the animal model to the average human. Another uncertainty factor of 10 accounts for human interindividual variation ranging from the average human to those at increased risk. The use of these two independent uncertainty factors provides protection for the normal and high-risk segments of the human population. The hormesis concept refines this traditional dose-response/risk management methodology. Calabrese and Baldwin (Calabrese and Baldwin, 2002) found that normal and high-risk subgroups display hormetic dose-response relationships, with the high-risk group's dose-response relationship being shifted to the left due to their enhanced susceptibility. An optimal dose for the normal population may be in the toxic zone for the high-risk group, whereas the optimal dose for the high-risk group may be without effect for the normal population. If the goal were to optimize the health response in the overall population, there would be a conflict between the two interest groups, the normal and those at higher risk. Under the nonhormesis scenario, there is no such conflict because the process is simply to lower the dose below predicted risks, ignoring possible benefits. Yet the hormetic dose response model is the more biologically plausible situation. Thus, it is expected that in the future regulatory agencies will have to address the issue of health optimization as a policy option on the basis of the hormetic dose response.



Table 3 Hormesis: How It Affects Biology and Medicine

<b>Impact on biological concepts</b>	
<i>Performance</i>	Low-dose stimulation is a measure of biological performance
<i>Plasticity</i>	The magnitude of the stimulatory response is an index of biological plasticity
<i>Allometry</i>	Hormesis responses conform to allometric analysis
<i>Adaptation</i>	Compensatory stimulation is a fundamental example of adaptation
<i>Evolution</i>	The hormetic response is highly conserved
<i>Stress</i>	Low-level stress optimizes system performance
<b>Impact on toxicology/pharmacology concepts</b>	
<i>Dose-response features</i>	There is a well-defined magnitude of stimulation
<i>Dose-time effect</i>	The time component is needed to study compensatory response
<i>Potency</i>	The hormetic response is independent of potency
<i>Hormetic synergy</i>	Defines chemical interaction below the threshold
<i>Mechanism strategy</i>	There are multiple proximate mechanisms of hormesis
<i>Study design</i>	Modest low-dose stimulation supports unbalanced study designs
<i>Study replication</i>	Increased need to demonstrate reproducibility of findings
<b>Environmental health risk assessment applications</b>	
<i>Validation of predictions</i>	Occur in observable zone; can be tested
<i>Predict and quantify harm below threshold</i>	No other model does this
<i>Predict and quantify benefits below threshold</i>	No other model does this
<i>Biological model selection</i>	Based on capacity to detect harm and benefit
<i>Harmonization of cancer and noncancer risk assessment via hormesis</i>	Occurs because dose-response characteristics of cancer and noncancer endpoints are similar with the hormetic model and independent of mechanism
<i>Change risk goals</i>	Optimizes population health, not only avoids harm
<i>Cost/benefit</i>	By including benefits hormesis, changes cost/benefit methods and strategies
<i>Biostatistical modeling</i>	Eliminates constraining models to pass through the origin
<i>Uncertainty factor application methodology</i>	Redesigned to optimize population health
<b>Medical implications</b>	
<i>Drug discovery and development</i>	The hormesis effect defines potential value

(continued)

Table 3 (continued)

<i>Therapeutic window</i> – The width of hormetic stimulation for performance endpoints
<i>Clinical trials</i> – Need to incorporate U-shaped dose-response relationships in study design
<b>Specific treatment areas</b>
<i>Aging</i> – Low doses of stress extend longevity via hormetic mechanisms
<i>Bone</i> – Biphosphonates act hormetically, strengthening bones at low doses
<i>Benign prostatic hyperplasia (BHP)</i> – Various drugs induce BHP via hormetic dose response
<i>Cancer</i> – Numerous antitumor drugs cause proliferation of tumor cells at low doses
<i>Cardiovascular disease</i> – Low doses of statins act via hormesis on the vasculature
<i>HIV treatment</i> – Low doses of antiviral drugs cause proliferation of the virus
<i>Memory</i> – The action of most memory drugs follow U-shaped dose-response relationships
<i>Neuroprotection</i> – Numerous agents protect neurons hormetically
<i>Ocular</i> – Low doses of drugs can enhance the risk of retinal detachment
<i>Pain</i> – Many pain-relieving drugs often act biphasically via hormetic mechanisms
<i>Priton diseases</i> – Antiprion drugs can enhance disease at low doses
<i>Sexual behavior</i> – Most drugs enhancing male sexual performance act hormetically
<i>Skin/hair</i> – Minoxidil grows hair via hormetic processes
<i>Antibiotics</i> – Low doses of many antibiotics may enhance bacterial colony growth at low doses
<i>Pulmonary hypertension</i> – Low doses of the widely used anxiolytic drug Prozac increase the risk of pulmonary hypertension in the fetus by enhancing the proliferation of smooth muscle in the pulmonary arteries
<i>Fibrotic conditions</i> (e.g., Dupuytren’s contracture of the hand) – Low doses of oxygen free radicals enhance the proliferation of human fibroblasts, leading to increased fibroblast density and pathological consequences

(continued)

Table 3 (continued)

<b>Agriculture and related industrial applications</b>
<i>Growth rates</i> – Low doses of stressor enhance growth in poultry
<i>Animal grazing</i> – Enhances plant productivity via hormetic processes
<i>Allelochemistry</i> – Chemicals released from plant roots act hormetically
<i>Pesticide drift</i> – Low doses of herbicides can enhance plant growth
<i>Crop production</i> – Hormetic mechanisms can increase growth
<i>Reduced diseases</i> – Plant diseases are reduced via hormetic mechanisms
<i>Microbial metabolism</i> – Hormetic mechanisms enhance greenhouse gas uptake in microorganisms
<i>Bio-fuel cells</i> – Hormetic mechanisms enhance hydrogen capture for bio-fuel cells in microorganisms
<i>Drug production</i> – Hormetic mechanisms enhance the synthesis of chemotherapeutic agents such as paclitaxel (Taxol)

## Discussion

This chapter has argued that hormesis is the most fundamental dose-response relationship based on the outcomes of several large-scale head-to-head comparisons with its rival dose-response models (Calabrese and Baldwin, 2003a; Calabrese and Baldwin, 2001; Calabrese et al., 2006) along with its substantial reproducible occurrence in numerous publications across the spectrum of biomedical subdisciplines. This represents a striking change in perception, given that the hormetic dose-response model had, throughout the last century, been nearly completely marginalized and dismissed. This change is particularly noteworthy because the dose-response relationship is the central principle of disciplines such as toxicology and pharmacology. When professional scientific groups make an error in the central core principle of their discipline, this is a cause of considerable concern, especially in light of their role in guiding society's decisions concerning drug discovery, the safety evaluation of chemicals and drugs, and governmental risk assessment practices, which affect the derivation of environmental, occupational, and food safety standards.

The basis of this error in the understanding, selection, and use of dose-response models was complex, deriving in large part from the long-standing and bitter dispute between homeopathy and traditional medicine (Calabrese, 2005a). It was also due to inherent challenges in studying the hormetic dose response, with its need for stronger study designs, greater statistical power, and reproducibility of findings, all due to the fact that the hormetic stimulation is modest and in need of more rigorous evaluation and documentation. By denying that there are treatment-related effects below the toxicological and pharmacological thresholds, the field of toxicology developed an incorrect understanding of the nature of the dose-response relationship.

This chapter has provided a new and improved concept of the dose-response relationship. That is, the most fundamental nature of the dose response has a toxic component that begins as doses exceed the toxic threshold and a performance stimulation component that begins immediately below the threshold. The dual nature of the dose-response relationship, with the low-dose hormetic stimulation representing biological performance, is a novel interpretation. The low-dose performance stimulation has unique characteristics, with its maximum being modest, usually only 30% to 60% greater than the control value. This performance feature of the dose response provides a quantitative estimate of biological plasticity throughout biological systems at all levels of organization. Thus, the hormetic dose-response relationship is a basic, unifying and explanatory biological concept, in addition to being an important quantitative tool for the assessment of drugs, chemicals, and radiation.

The presence of performance and toxicity features of the dose response has important implications for numerous biological and biomedical disciplines (Table 3). For example, at high concentrations, antitumor drugs inhibit cell proliferation of tumor cell lines and other types of cells, whereas at lower concentrations these agents often display a stimulatory effect consistent with the quantitative

features of the hormetic dose response. Similar responses also are commonly reported for antibiotics, antifungal agents, and antiviral drugs (Calabrese and Baldwin, 2003b). In a practical sense all medical treatments that are targeted for the toxicity zone of the dose-response relationship will eventually achieve a concentration within the hormetic or performance zone for a variable period of time due to pharmacokinetic factors. It is also important for those assessing the hazard potential of chemicals to define the entire dose-response continuum, which includes both the performance and toxicity dimensions. In general, the toxicological assessment of chemical agents only focuses on the above-threshold aspects of the dose response. Yet in all risk assessment practices, there are extrapolation procedures that estimate responses to doses far below the measured toxicological threshold without any information generated about the performance component of the dose response. In fact, the performance component of the dose response has been ignored in such cases under the incorrect assumption that it does not exist.

The overwhelming preponderance of evidence supports a conclusion that the long-revered threshold dose-response model fails to accurately predict responses in the below-threshold zone, that is, where people are routinely exposed. Continued reliance on this model to guide public regulatory judgments is no longer responsible public policy. Much evidence indicates that the hormetic dose-response model is highly generalizable and accurately predicts responses in the below-threshold zone, far outperforming the threshold and linear-at-low-dose models. Serious consideration should therefore be given to a major reevaluation of the continued use of current default dose-response models (i.e., threshold and linear) in the biological and health sciences, as well as in regulatory domains, especially in light of the failings of these models to predict low-dose effects, and their possible replacement with far more accurate and validatable models such as the hormetic dose-response model.

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