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HORMESIS: The Dose-Response Revolution

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■ **Abstract** Hormesis, a dose-response relationship phenomenon characterized by low-dose stimulation and high-dose inhibition, has been frequently observed in properly designed studies and is broadly generalizable as being independent of chemical/physical agent, biological model, and endpoint measured. This under-recognized and -appreciated concept has the potential to profoundly change toxicology and its related disciplines with respect to study design, animal model selection, endpoint selection, risk assessment methods, and numerous other aspects, including chemotherapeutics. This article indicates that as a result of hormesis, fundamental changes in the concept and conduct of toxicology and risk assessment should be made, including (*a*) the definition of toxicology, (*b*) the process of hazard (e.g., including study design, selection of biological model, dose number and distribution, endpoint measured, and temporal sequence) and risk assessment [e.g., concept of NOAEL (no observed adverse effect level), low dose modeling, recognition of beneficial as well as harmful responses] for all agents, and (*c*) the harmonization of cancer and noncancer risk assessment.

INTRODUCTION

Toxicology, as defined by Gallo & Doull (1), is the "study of the adverse effects of xenobiotics." This perspective is consistent with the later definitions of toxicology by Furst & Fan (2), Hayes (3), and others. The key term in this definition is "adverse." The term adverse is typically employed by regulatory agencies (e.g., U.S. EPA) in critical risk assessment related concepts, such as the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL). This most evident manifestation of the toxicological concept of adverse implies that toxicology is an above NOAEL discipline because it is the study of "adverse effects." It also implies that either there are no effects below the NOAEL or that they are not relevant to and/or part of toxicology.

Over the past five years, we have demonstrated that there are numerous responses to chemical/physical agent exposures that occur below the traditional NOAEL (4–11). These findings may also have profound effects on the health of the individual. Such findings challenge not only how we design experiments, integrate data, and apply biostatistical extrapolation models, but also how we define toxicology itself. In fact, these emerging data on the dose response strongly suggest

that the earlier definitional paradigms of toxicology that have guided the field for so long should be amended to the study of the "entire dose-response continuum." Besides suggesting that the definition of toxicology itself should be changed, where is the dose-response revolution leading us?

WHAT IS THE DOSE-RESPONSE REVOLUTION?

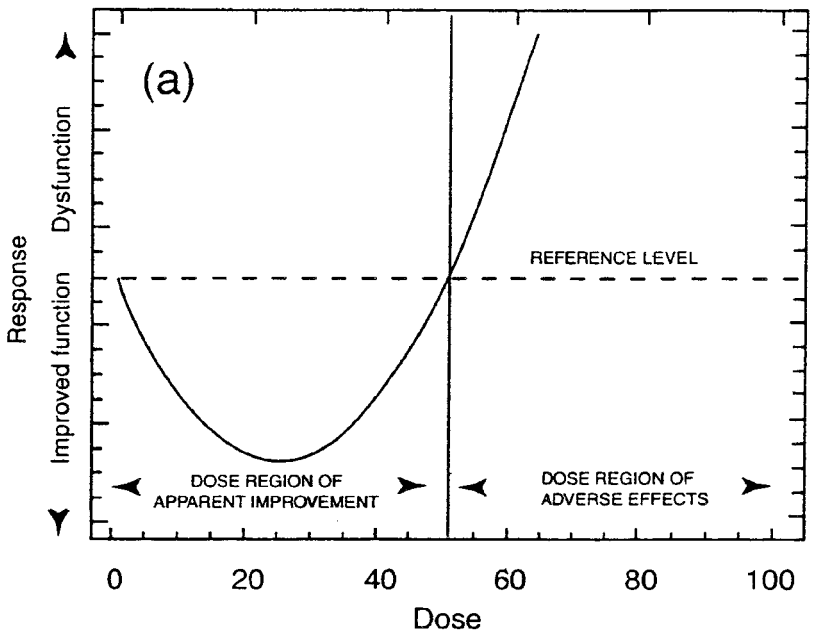
The dose-response revolution is the changing perception that the fundamental nature of the dose response is neither linear nor threshold, but U-shaped. The field of toxicology was lulled into the belief that these two ruling dose-response paradigms (i.e., threshold/linear) were universally valid in their respective domains and the only broadly applicable models relevant to federal risk assessment. The threshold assumption was steeped in common experiences of physical (e.g., melting and boiling points) and biological observations (i.e., vast numbers of studies assessing responses at high doses, constant hazard assessment preoccupation with NOAEL/LOAEL derivation, and the use of biostatistical models that were either emphasizing LD_{50} estimation or their application to extrapolate findings far beyond the observable range). In addition, endpoints, such as serum enzymes and hematological parameters, that are easily and reliably measured were emphasized in which thresholds were the dominant observation. This would also be the case with animal models in which background disease incidence was negligible for most organs in short-term studies (up to 13 weeks in duration). In the case of low-dose linearity, with cancer risks approaching 10^{-4} to 10^{-7}, this is a public health-motivated, theoretically based, biostatistical construct that is impossible to prove in any conceivable practical experimental setting. Despite its validation limitations, the assumption of low-dose linearity has become accepted and continues to dominate the actions of public health and environmental agencies.

The dose-response revolution argues that the toxicology community, including those in the regulatory-risk assessment domain, recognize the existence of U-shaped dose responses not only as real in specific cases but also as broadly generalizable. However, acceptance that hormetic-like U-shaped dose responses are widespread and real has been difficult to achieve. The reasons for this are many, but in general include the following. First, the field of toxicology has become progressively and insidiously dependent on the role of government to set the national (and international) toxicological agenda. This agenda translates into designing and interpreting studies to fit into current risk assessment paradigms. That is, in the case of noncarcinogens, regulatory agencies design hazard assessment methodology to provide a NOAEL, whereas in the case of carcinogens, the study needs data that can be employed to estimate low-dose cancer risk. Such NOAEL and/or low-dose evaluations are dominating concerns. These controlling governmental regulatory perspectives have provided a seductive focus on toxicological thinking, providing the flow of financial resources and forcing private-sector and academic institutions to respond to such initiatives. Second, there is fear among many within the regulatory community that acceptance of hormesis as a toxicological dose-response

principle implies that low doses of at least some, but most likely most, toxic substances may produce a beneficial effect at low doses, such as enhanced longevity or decreased disease incidence. This fear can result in a powerful emotional bias that can stifle objective assessment of toxicological data. Third, the belief in the universality of biological thresholds became firmly established and accepted by the scientific community and government public health/regulatory agencies during the early to mid decades of the twentieth century. These beliefs became codified in risk assessment/management procedures of the U.S. FDA and U.S. EPA and by comparable governmental organizations of other countries. These threshold beliefs were expanded in the 1970s to accommodate the acceptance of low-dose linearity for carcinogens. This codified governmental risk assessment procedure created inflexibility in dealing with challenges, and not just rare exceptions to the government's established paradigms. That is, once a procedure is established, it often takes an extraordinary amount of effort and data to effect a change by governmental agencies. This appears to be especially the case if the change has the support of the industrial sector. For example, it took over a decade of consistent findings for the EPA to accede to industrial pressure that chemically induced kidney tumors in the male rat due to chemically induced hyaline droplets were species/gender-specific and could not be reliably extrapolated to humans. The extraordinary and massive amount of research on this issue resulted in an agent-specific response victory but relatively minor conceptual concession by the EPA. The point is, once agencies fix a procedure it is nearly impossible to effect a change, even in the face of overwhelming data. Fourth, despite the above statements about hormesis being broadly generalizable and real, it is not actually seen too often. Its assessment requires stringent and powerful study designs with a large number of doses, above and below the NOAEL, properly spaced, and often with a temporal component. Put quite simply, such studies are in a small minority, thus explaining its low visibility. In fact, only 1%–2% of toxicological studies over the past 30 years have satisfied the needed rigorous entry criteria to even begin to assess whether hormesis exists or not (12). Fifth, the low-dose stimulation is quite modest, being at maximum only approximately 30%–60% greater than controls (4, 5, 12). When one combines the inherent bias against hormesis that denies its existence or rejects its implications with the fact that most studies cannot even study hormesis, it simply reinforces the initial bias.

EVIDENCE FOR THE EXISTENCE OF HORMESIS

In 1996, we received a grant from the Texas Institute for Advanced Chemical Technology (TIACT) at Texas A&M to assess whether the hormesis hypothesis was toxicologically credible. We set forth to make initial judgments on the existence of hormesis based on the conformity of published dose responses to the hormetic β-curve (Figure 1). In order to assess this in an objective manner, we developed a priori criteria based on study design features, quantitative characteristics of the dose response, statistical power, and reproducibility of experimental findings. These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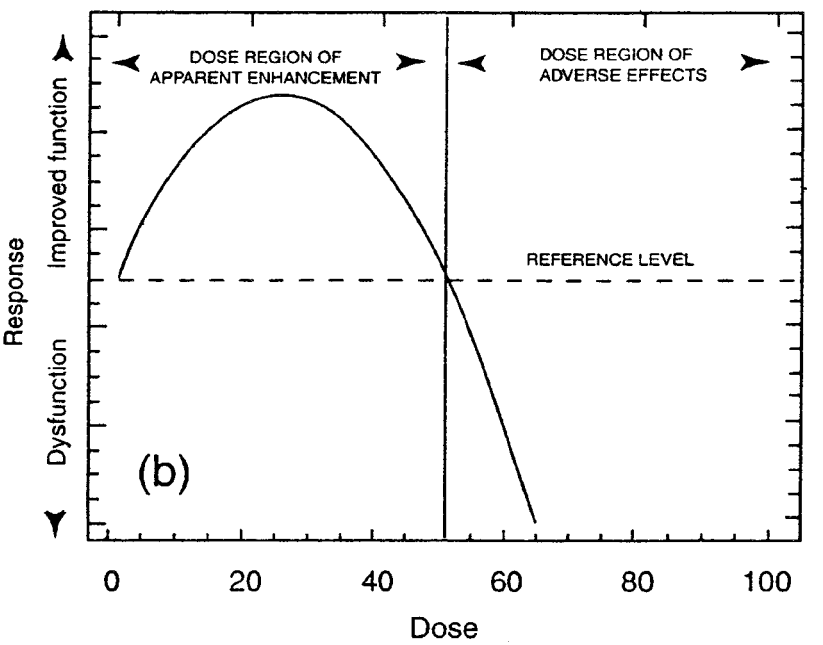
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concepts were transformed into a mathematical algorithm and then applied to thousands of toxicology investigations (4, 5). We determined that a large number of toxicology studies expressed dose-response relationships of an hormetic-like biphasic nature. These findings revealed that such effects were not only common but seen across chemical class and physical stressor, animal model, age/gender of subject, and biological endpoint, and therefore, broadly generalizable (Figure 2). We also discerned the quantitative features of the hormetic dose response. The amplitude of the hormetic response was inherently modest, almost never exceeding a factor of twofold greater than the control, but usually no greater than 130%–160% of the control. The width of the low-dose stimulatory range was approximately 10-fold, being contiguous with the NOAEL. In general, approximately 70% of the several thousand examples were equal to or less than a factor of 20, whereas 95% were within a 100-fold range. On rare occasions (∼2%), the width of the stimulatory range did exceed 1000-fold (Figure 3) (30, 31).

Although this information was important in establishing the toxicological reality of hormesis and some of its dose-response features, it was legitimately criticized by Crump (32) for not providing a frequency estimate of hormetic responses in the toxicological literature. As a result of these initial limitations, we established rigorous a priori entry and evaluative criteria to assess the frequency of hormesis in the toxicological literature. Over 20,000 articles were evaluated from the mid-1960s to the late 1990s, with only 1.5%–2.0% of studies being able to satisfy entry criteria to assess hormesis as an hypothesis (12). However, of those that did pass the entry criteria (i.e., having an appropriate study design), approximately 40% satisfied the evaluative criteria (i.e., the functional definition of hormesis).

In addition to satisfying entry and evaluative criteria for hormesis, a complementary perspective on the issue of whether the low-dose stimulation could have occurred by random process was devised. Of the nearly 1800 doses below the NOAEL, an assessment was made of the proportion of responses that statistically significantly differed from the control in the direction of hormesis or in the opposite direction. If the responses were random, one would expect that the response would vary similarly for either possibility. However, responses displaying statistical significance in the hormetic direction occurred 32 times more frequently than the opposite! Thus, these findings strikingly support the conclusion that the hormetic responses cannot be explained by random processes (12).

Further extending the evidence on the occurrence of hormesis is that we have recently completed an assessment of the occurrence of hormesis within the NTP

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Figure 1 (*a*) General form of U-shaped dose-response curve showing response relative to a reference level, with a region of apparent improvement (e.g., reduction in dysfunction) as well as a region of toxic or adverse effects. (*b*) Reciprocal of the same curve showing a region of apparent enhancement (e.g., increase above normal level of function) as well as a region of toxic or adverse effects. From Davis & Svendsgaard (13).

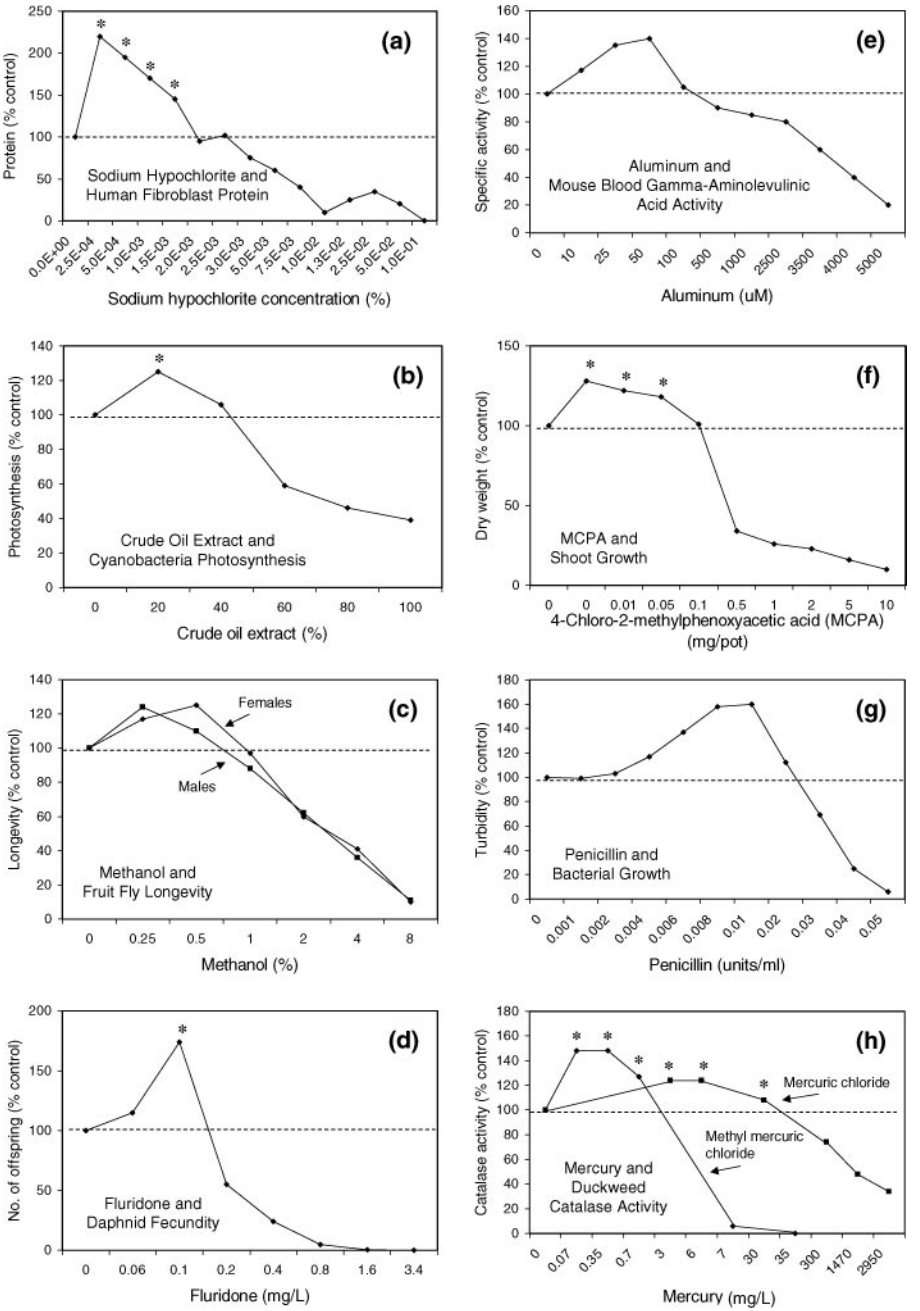

Figure 2 Representative examples of inverted U-shaped dose-response relationships displayed by a variety of experimental models and chemical agents. The asterisks indicate statistically significant data ($^{*} = P \leq 0.05$, $^{**} = P < 0.01$, $^{***} = P < 0.005$). Absence of statistical significance denotes studies that did not perform statistical analyses on their data. Sources of data for (*a*)–(*p*) are References 14–29, respectively.

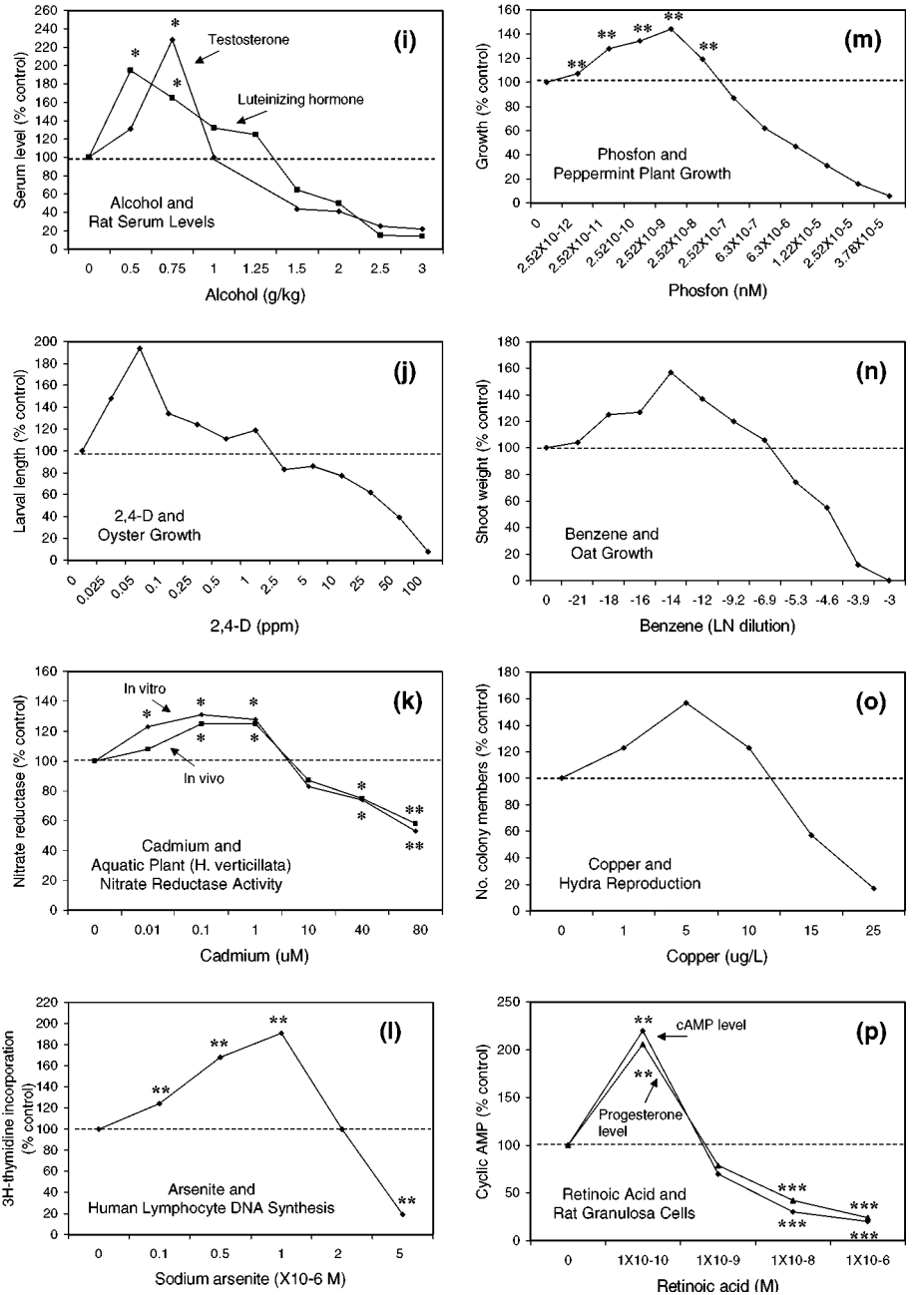

Figure 2 (*Continued*)

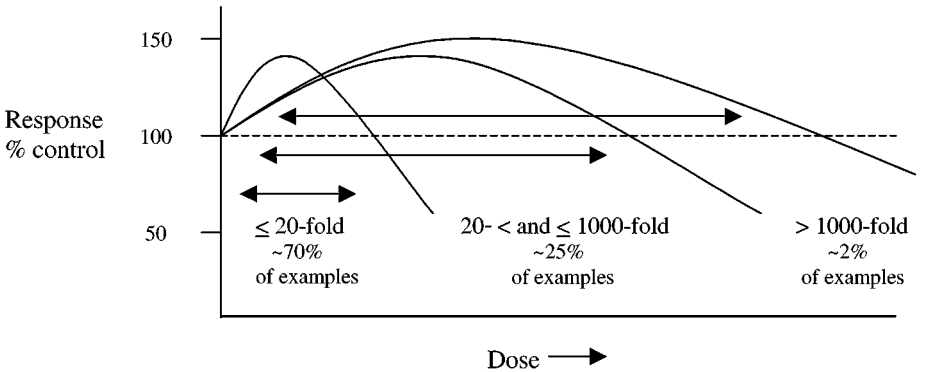

Figure 3 Stylized dose-response curves reflecting the relative distribution of stimulatory dose ranges. Note the maximum stimulatory response is usually 130%–160% of the control value regardless of the width of the stimulatory dose range; the inverted U-shaped curve was used for illustrative purposes only, whereas examples in the hormesis database include both inverted U- and U-(J-) shaped curves depending upon the endpoint measured. Modified from Calabrese (30).

dose-range finding studies (E.J. Calabrese & L.A. Baldwin, in preparation). In this assessment, hormetic responses satisfying our previously employed a priori evaluative criteria (4, 5) revealed hormetic responses in over 60% of studies involving male mice and over 40% involving female mice. These observations are particularly significant because they represent findings from the extensive, carefully overseen and reviewed U.S. government toxicological testing program.

The next criticism affecting the acceptance of hormesis was then put forth by Klaassen (33), who indicated the need to demonstrate underlying mechanism(s) in order for hormesis to gain credibility. To this end, we had obtained evidence, especially in the pharmacological literature, that provides mechanistic explanations to account for many hormetic biphasic dose responses. More specifically, we have evidence accounting for hormetic responses at least to the receptor level, but frequently at levels of further complexity, for nearly 30 different receptor systems (Table 1). In these investigations, we find that investigators typically made use of synthetic agonists/antagonists to dissect and then reconstruct their reported biphasic dose responses (34). It is important to note that such dismantling of the dose response within experimental pharmacology has rarely been reported in the toxicological literature. Thus, the mechanism argument against the hormetic hypothesis, like that of the frequency issue, is no longer tenable. The key conclusion revealed by the numerous mechanistically oriented investigations is that there is no single hormetic mechanism. Each endpoint considered in an hormetic evaluation may be affected by a different receptor system (or by interacting receptor systems). What each mechanism does have in common is the quantitative feature of the dose-response curve; that is, the amplitude and range of the

TABLE 1 A partial listing of receptor systems displaying biphasic dose-response relationships

Receptor systems displaying biphasic dose-response relationships	
Adenosine	Neuropeptides[1]
Adrenoceptor	Nitric Oxide
Bradykinin	NMDA
CCK	Opioid
Corticosterone	Platelet-derived growth factor
Dopamine	Prolactin
Endothelin	Prostaglandin
Epidermal growth factor	Somatostatin
Estrogen	Spermine
5-HT	Testosterone
Human chorionic gonadotrophin	Transforming growth factor β
Muscarinic	Tumor necrosis factor α

[1]For example, substance P and vasopressin.

Abbreviations: CCK, cholecystokinin; 5-HT, 5-hydroxytryptamine (serotonin); NMDA, N-methyl-p-aspartate.

low-dose stimulatory response and its relationship to the NOAEL are strikingly alike regardless of agent, model, and endpoint. This strongly supports the conclusion that the hormetic process represents a common strategy for resource allocation when systems need to respond to low-level metabolic perturbations. Thus, we believe that continuing to search for/demand a single molecular explanation (i.e., toxicological Holy Grail) to account for hormesis is a belief in an incorrect paradigm.

The next argument employed against accepting hormesis (at least as broadly generalizable) is that there is unconvincing evidence that it is operational for mutations and cancer (35, 36). Although there are unique challenges facing hormesis in terms of these endpoints (e.g., typically very high doses in cancer bioassays, limited number of dosages, use of models with very low background tumor incidence), there are a substantial number of cases in the literature that document hormetic responses for the various stages of the process of carcinogenesis, including tumor formation. This is the case for both chemical- and radiation-induced tumors (37, 38). These findings indicate that the concept of hormesis is compatible with the dose response for chemical- and radiation-induced tumorgenicity. The examples discussed here are not trivial cases, but ones that are reported from highly experienced and respected laboratories, passing rigorous peer review in the most highly regarded journals. Especially in the case of radiation, the experiments have been particularly robust, often having many hundreds, sometimes up

to several thousands, of animals/dose, sample sizes far exceeding those employed in the U.S. NTP bioassays. In fact, in the case of Ullrich & Storer (39), 15,562 mice were employed over seven treatments plus control in assessing the effects of gamma radiation of lung tumor incidence in the female RFMf/Un mouse [see (38), Table 1, p. 331].

WHEN IS ENOUGH EVIDENCE ENOUGH?

Although we believe that the accumulated evidence is overwhelmingly sufficient to establish hormesis a secure place in toxicology, including its ample presence in basic toxicology texts, a critical issue is what role should hormesis play in risk assessment. The principal question is whether hormesis should be proven on a case-by-case basis or should it be accepted as a default assumption. To establish hormesis on a case-by-case basis would require a substantial change in how hazard assessment is conducted. It would affect the number of animals/treatment, selection of endpoints to be measured, as well as the specific animal model. It would also affect the need to demonstrate replication of critical findings because hormetic responses are generally modest. The establishment of a case-by-case approach for the acceptance of hormesis for regulatory purposes, while appearing quite rational and the proper path to proceed, would essentially derail the hormesis concept for widespread practical use in risk assessment. The evidence supporting the generalizability of the hormetic model is sufficiently convincing. Of particular importance to the current discussion is that we have demonstrated that the hormetic model occurs with significantly greater frequency as compared with the traditional threshold model, thereby arguing for its acceptance as the principal dose-response default option. This conclusion is further emphasized in practice because biostatistical approaches cannot preferentially distinguish among possible dose-response models for most individual experiments given the limitations in experimental design. Thus, it is necessary to consider data from the broad body of available studies to derive toxicology-based default assumptions. On scientific grounds, therefore, the hormetic model should strongly prevail over its rivals.

In discussion of high-profile carcinogens, such as dioxin and arsenic, the concept of hormesis is often raised. Although there is evidence supporting hormesis in both cases [dioxin (40, 41) and arsenic (42–44)], the more appropriate and defensible position is to require detailed consideration of the broad-based findings on hormesis. To limit the argument for hormesis to a simplified agent only restricts the use of available data and inevitably forces a decision based on a more limited and insecure foundation. Second, the default should incorporate the concept of the most biologically plausible toxicological outcome rather than a philosophy of minimization. As is now being seen in multiple dimensions of the biomedical community, minimization is giving way to optimization for endpoints, such as cholesterol, blood pressure, body weight, exercise, as well as bilirubin and the theoretically important domain of reactive oxygen species (45–47).

THE CONCEPT OF HORMESIS IS STRENGTHENED BY ITS OCCURRENCE IN NONTOXICOLOGICAL FIELDS

The significance of a biological concept is often judged by its generalizability and the extent to which it may affect related disciplines. In this case, the hormetic concept provides numerous applications in multiple areas of the biological sciences as well as providing a basis for theoretical foundations within the broad evolutionary, biological-toxicological-medical continuum. Several examples illustrate the rich generalizability of the hormesis concept.

Experimental Psychology

A well-known "law" in experimental psychology, the Yerkes-Dodson Law, describes a dose-response relationship that is similar in its qualitative and quantitative features to hormesis. Robert Yerkes, the famous Harvard psychologist after whom the Yerkes Primate Center in Atlanta was named, and his graduate student, John Dodson, reported in 1908 that learning performance by rodents was optimized by a modest amount of stress but diminished at either too low or excessive stress (48). Furthermore, these investigations altered the quantitative features of the dose response (i.e., width of the stimulatory enhancing zone) by changing the complexity of the task. This observation is of considerable interest because it provides an experimental model to assess and manipulate a quantitative dimension of the dose response. The Yerkes-Dodson phenomenon has been repeatedly observed over the past century and has been routinely discussed as a general phenomenon in numerous introductory psychology texts (49). More recent investigations have explored the suggestion that such behavior may be related to endogenous alterations in corticosterone concentrations and have reconstructed the biphasic dose response of the more descriptive studies in relationship to endogenous biphasic changes in corticosterone levels (50). The implications of the Yerkes-Dodson Law are substantial, affecting optimal workplace strategies, learning environments, accuracy of eyewitnessing at different levels of stress, and numerous other aspects.

Plant Biology

ALLELOPATHY This area of plant biology studies the effects of root exudates on the surrounding microorganisms and plants. Numerous experimental studies have revealed that the effects of such exudates on a wide variety of species displays hormetic-like biphasic responses (51–53). These observations are noteworthy because they suggest that hormetic effects may be instrumental in affecting the occurrence of primary and secondary succession of ecological systems. Furthermore, numerous investigations have begun to utilize the concept of hormesis within the context of allelopathy to develop natural product-based herbicides. However, in this case the focus would be on the upper (i.e., toxic) end of the dose response.

SYNTHETIC HERBICIDES Numerous synthetic herbicides induce hormetic effects in target plant species. Large-scale screening of chemical agents has consistently revealed the capacity of herbicidal agents to induce biphasic dose-response relationships of an hormetic nature (19, 54–56). The findings that low doses of herbicides can stimulate plant growth have important implications concerning herbicidal drift and their effects on adjacent crops.

Chemotherapy

Numerous chemotherapeutic agents display hormetic responses. These include antibacterials, antivirals, antitumor, and antiangiogenesis agents, as well as agents such as minoxidil, which may stimulate hair growth. The quantitative and temporal features of the dose response for chemotherapeutic agents are similar to that reported for both chemicals and radiation. The clinical recognition of the significance of the hormetic features of the dose response of therapeutic agents has been greatly underappreciated, typically due to the focus on the high-dose functions of the drug, ignoring the low-dose enhancing on the virus, bacteria, fungal, or tumor growth.

The implications of hormetic effects for chemotherapeutics also extend to the domain of peptide biology and its relationship to the human genome. Numerous hormetic-like biphasic dose responses exist for peptides, further displaying the broad generalizability of the hormetic concept. Recent assessments of both chemotherapeutic (57) and peptide (58) examples of hormetic effects have been completed.

RISK ASSESSMENT

In this section, the implications of hormesis are explored in the area of environmental health/toxicology as well as within the more broadly based biomedical sciences.

Hazard Assessment

If hormetic effects are an evolutionary/biological/toxicological expectation, then it implies that hazard assessment strategies include a protocol to assess its possible occurrence. This has practical importance because hormetic effects may affect both the concept and derivation of the NOAEL. The derivation of the NOAEL could change if the low-dose stimulation were determined to be an adverse effect. The hormetic dose-response continuum in this instance (i.e., both the increase at low doses and the decrease at high doses from the control) could be viewed as adverse. However, if the low-dose stimulation were deemed as beneficial, it would have little direct effect on the concept of the NOAEL, but could affect how the traditional NOAEL is derived (59) as well as challenging the basic goal of the risk assessment process from the exclusive focus on the avoidance of potential harm to also include the concept of benefit.

Within a traditional public health framework, beneficial effects may be reasonably and unambiguously identified. For example, such responses could include:

- increased average lifespan
- reduced incidence of tumors
- reduced incidence of birth defects
- reduced incidence of various diseases and illnesses
- enhanced learning and other positive behavior performances.

Adverse health effects would simply be responses opposite to those established as beneficial. However, there would be a number of responses that would be difficult to resolve and classify as beneficial or adverse without more detailed assessment. Such responses could include, but not necessarily be limited to, increased organ weight, increased body weight gain, increased fecundity, and increased immune responsiveness [see (60) for a more detailed discussion of these endpoints in relation to hormesis].

The capacity of assessing hormesis within the context of these endpoints and their public health meaning requires the careful selection of animal model along with appropriate study design. In general, current models and experimental protocols are generally ill equipped to accomplish this essential task.

Although it may be desirable to demonstrate the existence of hormesis for each agent tested for all endpoints of concern, this may be an infeasible objective with respect to time, money, and model limitations. If this were the case, it is recommended that one consider the possibility of accepting the hormetic expectation as a default assumption (60).

Agencies like the EPA commonly employ default assumptions in exposure, hazard assessment, and risk assessment assumptions. In most of these matters, the amount of available evidence is far less than that available for hormesis. Furthermore, our collective information confirms that among the available toxicological models, the hormetic one is the most predominant.

The recognition of the impact of hormesis on the risk assessment process has the potential to broaden study goals of the hazard assessment process. That is, besides defining the upper end of the dose-response continuum [NOAEL-LOAEL-FEL (Frank Effect Level)], additional doses could be directed to defining the subNOAEL response zone. In addition, because hormetic responses are likely to be modest (i.e., no greater than 130%–160% of the control), this would have important implications for sample size and statistical power issues. Likewise, in order to affirmatively address the possibility of hormesis, it is necessary to consider the issue of background disease incidence and animal model selection. In practice, it has been desirable to use models that are reasonably susceptible to develop agent-induced disease while having a low background incidence. Assessing hormesis has only been possible for a few selected endpoints in chronic bioassays, that is, when the background incidence is high (e.g., testicular cancer in the F344 male rat, mammary tumors in the Sprague-Dawley female rat).

Risk Characterization

The risk assessment implications of hormesis are varied, complex, and may be seen whether the context is evaluating noncarcinogens or carcinogens.

NONCARCINOGEN RISK ASSESSMENT In the case of noncarcinogen risk assessment, the current EPA methodology is limited to NOAEL derivation, the application of uncertainty factors (UFs) to derive a reference dose (RfD), and the application of a relative source contribution. The standard derivation process uses a risk management plan that ensures that a regulated agent would not have a harmful effect on the general public as well as most members of the high-risk subsegment of the population. The hormesis concept provides a series of new risk management options to decision makers. In this case, if low-dose stimulatory responses were assumed to be beneficial, the decision maker could view hormesis as adding potential benefit to society and could estimate an optimized population-based exposure standard. Although this could be a complex and, indeed, controversial approach, it is of more than academic interest. It would seek to estimate not a de-minimus risk, but an optimized population-based beneficial dose. The de-minimus risk option that has guided essentially all environmental regulatory agencies places its entire emphasis on avoiding harm, lacking consideration of affirmative benefit. The optimized benefit approach would be based on the concept of hormesis and integrate data from the range of risks and benefits to estimate an exposure standard. A methodology to estimate a so-called optimized benefit dose would need to quantitatively integrate information on the dose-response continuum for the normal and high-risk subsegments of the population, their relative proportions in populations, and the cost-benefit relationship for the relevant endpoints at each dose. Even if this approach were not employed, it would be critical for decision makers to be aware of such information.

CARCINOGEN RISK ASSESSMENT In the area of carcinogen risk assessment, hormesis could have a very significant practical impact. Because the hormetic concept assumes the existence of thresholds at doses higher than the hormetic zone, the acceptance of hormesis could change the current practice of cancer risk assessment. However, it is important to recognize that current EPA cancer risk assessment methodology assumes that the human and animal models are equally susceptible. This is in contrast to the noncancer assessment process in which humans are assumed to be 10-fold more sensitive. Acceptable exposures in the case of noncarcinogens are derived by UFs, whereas in the case of carcinogens, acceptable exposures are derived by conservative low-dose extrapolation modeling. Sielken & Stevenson (61) have provided a detailed consideration of how quantitative risk assessment for carcinogens could be made responsive to the concept of hormesis. Such changes are summarized in Table 2. The fact that hormesis infers thresholds for both cancer and noncarcinogen endpoints and that they display similar quantitative features of the hormetic dose-response continuum

TABLE 2 How quantitative risk assessment could be made responsive to the concept of hormesis [adapted from Sielken & Stevenson (61)]

Recommendations for incorporating hormesis into risk assessment
Dose-response models should have greater flexibility to fit the observed shape of the dose-response data; such models should not be constructed to be forced to always be linearly decreasing at low doses
Hazard assessment evaluations should incorporate greater opportunity to identify the hormetic portion of the dose-response relationship
New dose metrics should be used that incorporate age or time dependence on the dose level rather than a lifetime average daily dose or its analog for a shorter time period
Low-dose risk characterization should include the likelihood of beneficial effects and the likelihood that a dose level has reasonable certainty of no appreciable adverse health effects
Exposure assessments should fully characterize the distribution of actual doses from exposure rather than just the upper bounds
Uncertainty characterizations should include both upper and lower bounds
Risk should be characterized in terms of the net effect of a dose on health instead of a single dose's effect on a single disease endpoint (i.e., total mortality rather than a specific type of fatal disease)

indicates a toxicologically based means to harmonize cancer and noncancer risk assessment.

USE OF HORMESIS TO HARMONIZE CANCER AND NONCANCER RISK ASSESSMENT

The differences in risk assessment methodologies to assess risk from exposure to carcinogens and noncarcinogens are striking. The basic assumption underlying the differences in risk assessment approaches for carcinogens and noncarcinogens is that they display fundamentally different dose-response relationships—one being linear at low doses, the other acting via a threshold. An assessment of the hormesis literature indicates that the dose-response relationship of chemical/radiation-induced cancer responses (Figure 4) and that of noncancer responses (Figure 2) are fundamentally U-shaped. Furthermore, the quantitative features of the dose-response in both instances are similar [e.g., amplitude and range of response, relationships to the zero equivalent point (i.e., ZEP, the highest dose showing a response equal to the control response)]. These quantitative features are also independent of the specific toxicological/pharmacological mechanisms. This observation has been essentially overlooked during the wide-ranging discussions concerning the cancer/noncancer harmonization process. If the fundamental dose-response relationship unity via the hormetic paradigm had been recognized in the mid-1970s, it is likely that an integrated risk assessment framework could have been constructed. Nonetheless, if harmonization is to effectively proceed, regulatory scientists need to address the issue of hormesis.

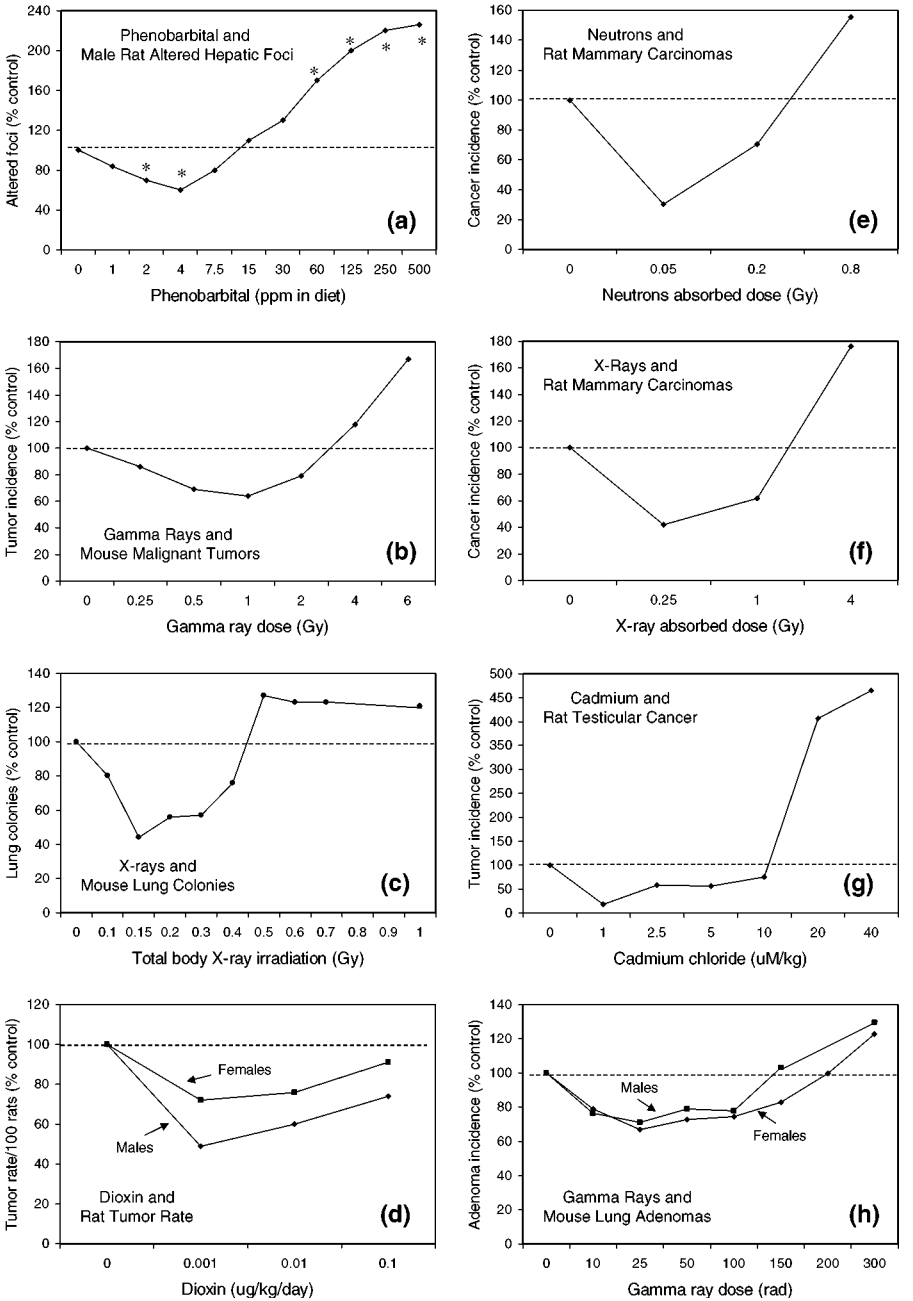

Figure 4 Representative examples of U- (or J-) shaped dose-response relationships of cancer responses induced by various radiation sources. The asterisks indicate statistically significant data ($^{*} = P \leq 0.05$, $^{**} = P < 0.01$). Absence of statistical significance denotes studies that did not perform statistical analyses on their data. Sources of data for (*a*)–(*d*) are References 62–65; for (*e*) and (*f*), Reference 66; for (*g*), Reference 67; for (*h*), Reference 39; and for (*i*)–(*l*), References 68–71.

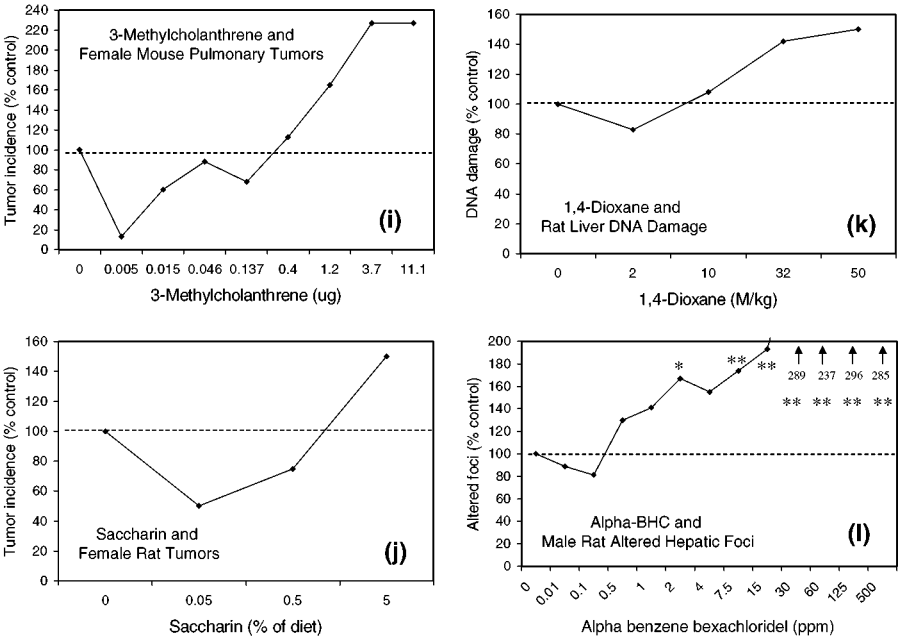

Figure 4 (*Continued*)

Risk Communication

Hormesis presents unique challenges for the discipline of risk communication (72, 73). This is particularly the case when the low-dose stimulatory response is viewed as beneficial (e.g., reduced disease incidence, enhanced longevity). Over the past 30 or more years, the goal of public health and environmental health education has emphasized concepts of nonthreshold for carcinogen responses, thresholds for noncarcinogens using the NOAEL, and no such thing as a beneficial effect from a nonnutritive pollutant. In the case of hormesis, each of these central, public, and environmental health dogmas are turned upside down. Such radical changes in low-dose risk assessment are likely to pose an enormous challenge to the acceptance of hormesis. Acceptance of hormesis will be difficult, therefore, because:

- Agencies will need to accept the possibility (actually, the likelihood) that toxic substances, even the most highly toxic (e.g., cadmium, lead, mercury, dioxin, PCBs, etc.) can cause beneficial effects at low doses.
- Hormesis will likely be seen as self-serving for the chemical industry.
- Elected administrations, whose EPA accepts the concept of hormesis as central to hazard/risk assessment, will be strongly attacked. This recently happened to John Graham in his senate confirmation hearings when he suggested that dioxin may exhibit such characteristics.

- The public may be very confused because the entire educational/public media on environmental issues had always characterized pollutants as harmful.
- Many industries thrive on environmental fears, such as companies featuring asbestos and radon remediation. This would also be the case of soil and other types of remediation technology-driven industries.

Despite these impediments to the acceptance of hormesis (even in the presence of compelling data), there are activities that suggest that the hormesis concept could be embraced by society. The widely accepted and well-established observation that ingestion of a daily glass or two of red wine reduces the risk of cardiovascular disease may have preconditioned society to consider the hormetic hypothesis for pollutants and radiation. In addition, the recognition that anticancer agents can both stimulate and inhibit tumor growth via an hormetic dose response may enhance the clinical interest in this concept.

Legal Implications

The legal implications emerging from the concept of hormesis remain to be more fully explored. However, the concept of hormesis has begun to be addressed by legal scholars (74). Of particular interest has been an exploration of the potential means to incorporate the concept of pollutant-induced beneficial effects in the risk assessment and cost-benefit process. Within this general framework, the District Court forced the EPA to recognize the beneficial effects of ozone pollution on the risk of UV-induced skin cancer in its overall assessment of the health effects of ozone (75, 76).

DISCUSSION

Hormesis is a toxicological concept that has been marginalized for over the past 70 years by several generations of toxicologists, although there is distinct evidence that this is changing. Although there are multiple reasons for this marginalization, the principal explanation results from the emphasis on high-dose testing in the historical and recent past, and the inadequacy of the vast majority of toxicological study designs to assess sub-NOAEL (ZEP) responses. Like most ideas, hormesis will become adopted only if it offers an improved explanation or means to solve problems. Whereas interest in low-dose stimulation in the 1920s, especially for radiation, was often generated by the search for medical elixirs, interest in hormesis in the 1990s was in response to governmental cancer risk assessment methods and policies that adopted the use of low-dose linearity and the linkage of such risk estimates to extremely expensive environmental clean-up standards. Hormesis has been seen as a direct challenge to low-dose linearity because it asserts the existence of thresholds. However, the significance of hormesis involves much more than cancer risk assessment, for it can affect how hazard assessment is performed (e.g., study design, sample size, dose selection, model selection, and which endpoints

are measured). It can also affect noncancer risk assessment, especially with respect to the concept and derivation of the NOAEL.

Hormesis is also influencing much larger biological/ecological and biomedical domains, the extent to which is grossly under-recognized. For example, hormetic-like biphasic dose-response relationships are also seen in essentially all pharmacological receptor systems (Table 1). Recognition that endogenous and exogenous agonists/antagonists display hormetic dose-response relationships may affect not only pharmacological experimentation but also clinical practices. Numerous examples exist that indicate that agents that are antagonists at high doses may become partial agonists at lower concentrations following an hormetic dose response. This implies that the same agent used to treat tumors at high concentrations may enhance their growth at lower concentrations. These dose-response features are critical to recognize. As hormetic-like biphasic dose responses become progressively more recognized and appreciated, they will improve research methods in toxicology, risk assessment procedures, chemotherapeutic methods, and drug development, as well as fundamental insights to evolutionary biology. We believe that the substantial and mounting data in support of the hormetic perspective are in the early stages of affecting such a profound series of changes in the biomedical/toxicological sciences that it will be seen as a true dose-response revolution, affecting a tidal-shift in toxicological perceptions, principles, and activities.

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