Getting the Dose-Response Wrong:

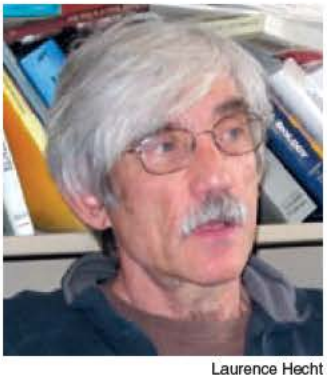
Although there were no adverse health effects from the 1979 accident, Three Mile Island became a symbol of fear for irrational environmentalists.

A Costly Environmental Problem

by Edward J. Calabrese, Ph.D.

The dose-response, the amount of a substance that causes a particular reaction, is the central pillar of toxicology, pharmacology, therapeutic medicine, and risk assessment. Getting the dose right is critical for patient health but also for public health, as reflected in community and occupational health standards. This might seem to be an easy task, but this hasn't been the case. The problem is that toxicological testing and the government version of it, called risk assessment, has been built upon the idea that all one needs to know can be derived from the testing of very few doses (for example, two or three) at very high levels of exposure; that is, the maximum amount that can be tolerated by mice or rats without obvious illness. This is the testing strategy by which chemicals are regulated by U.S. agencies like EPA (Environmental Protection Agency) and OSHA (Occupational Safety and Health Administration) and from which community and occupational health standards are derived.

The current method for risk and safety assessment for environmental substances is seriously flawed, because it does not consider effects at low-dose exposure.



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Dr. Edward Calabrese is Professor in the Environmental Health Sciences Division at the University of Massachusetts at Amherst. He is a toxicology specialist, who has written extensively on the non-linearity of dose-response, including the benefits of low-dose radiation, called hormesis. He is founder and chairman of the advisory committee of BELLE, the Biological Effects of Low Level Exposure, a group founded in 1990, which includes scientists from several disciplines and aims to encourage assessment of the biological effects of low level exposures to chemical agents and radioactivity. Dr. Calabrese explained in an interview with 21st Century Science & Technology, *published in the Fall 2011 issue, that today's environmental policies are based upon the lie that there is no safe dose of radiation. This has led to an irrational fear of radiation and of nuclear power, depriving millions of both nuclear energy, and the health benefits of hormesis.*

The problem with the above hazard assessment scenario is that the vast majority of people live in a world of very low exposures. The challenge is to ensure that regulatory agencies can accurately extrapolate their findings at very high doses to those at very low levels. The magnitude of such extrapolations can be highly variable, ranging from "only" several thousand-fold to well over a million-fold, depending on the chemical tested and the animal model used. It is similar to long-range weather forecasting: The longer out the forecast period goes, the greater the uncertainty. Thus, the decision of what is the so-called "right dose" becomes model-based. That is, a biostatistical model, rather than experimental results, is used to estimate responses in the low-dose zone, which suggests the further question of what is the "right model."

During the early to middle decades of the 20th century, the combined fields of medicine, pharmacology, and toxicology determined that the most fundamental dose-response model was the **threshold model**—below a certain threshold, there are no discernible effects; above it, biological effects occur. The threshold model resonated consistently well with personal experience, and there was also a fair amount of experimental data that appeared consistent with it. These factors helped shape the interdisciplinary consensus that made the threshold dose-response the standard basis for hazard assessment protocols for testing all drugs, chemicals, and commercial products and for the derivation of occupational and community health standards.

The threshold model was simple to understand, easy to accept, and easy to implement: "Threshold" indicated that biological changes can be induced only once a certain level of exposure was exceeded. Below that level, or threshold, no significant biological changes take place, only background noise. Exposure above that threshold would initiate a process of pharmacological activity in the case of drugs, or toxicity for chemicals. On the pharmacological side, it was thought that many drugs would act only after a certain number of receptors on or in a cell had been activated. In the case of toxicity, the threshold would be passed when the repair processes were exceeded.

The Biphasic Dose Model

Although this simple explanation provided the theoretical and empirical basis to support the threshold dose-response model, its acceptance became complicated by two troubling facts: It failed to be validated experimentally, and it was in an ongoing competition with the **biphasic dose model**. In this model, the biological effects below a certain threshold were often seen to be beneficial, while those above the threshold were detrimental. Historically, the biphasic dose-response model was nest-

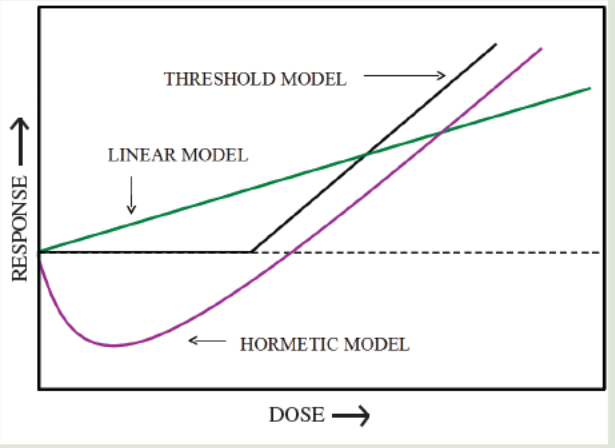

Figure 1
Comparison of the Three Most Dominant Dose-Response Relationships in Toxicology and Pharmacology

Threshold dose-response model—This dose-response describes a relationship when a drug or toxic substance shows a response only after a certain dosage has been exceeded. Below that transitional dose (i.e., threshold) no biological response occurs due to exposure to the agent under study. The only changes observed in the below threshold dosage zone (i.e., low dose zone) would be due to normal background variability.

Linear dose-response model—This dose-response describes a relationship in which the response is directly related to the dosage. In this case, there would be no safe exposure to a toxicant or carcinogen. Taken to its extreme, it suggests that even a single molecule (or ionization, in the case of radiation), could initiate the disease process, including cancer. This is an assumption that is used by regulatory agencies in the United States for genotoxic chemical carcinogens and ionizing radiation.

Hormesis dose-response model—This dose-response describes a specific type of *biphasic dose-response*. A biphasic dose-response occurs when both a stimulation and an inhibition are represented. The hormetic-biphasic dose-response is one which has a unique quantitative description. That is, its amplitude and width of the stimulatory response are constrained to be within specific limits. In addition, the stimulatory response has a specific quantitative relationship to the threshold value. These features result in making the hormetic dose-response a specific type of biphasic dose-response. It is a more precise descriptor of the biphasic dose-response and therefore is extremely useful.

ed within the conflict between traditional medicine and homeopathy. By the early 1900s, the biphasic dose-response model was called the Arndt-Schulz Law and also Hueppe's Rule, after its discoverers. However, in 1943, it received the description "hormesis" from the Greek word "to excite" by two University of Idaho mycology researchers, as will be discussed below (Calabrese 2011a).

Among the different investigators, the primacy of the discovery of the hormesis concept, and its long-standing articulation and defense, go to Hugo Schulz, a Professor of Pharmacology and Toxicology at the University of Greifswald in Northern Germany (Calabrese 2009a). The moment of discovery, as recaptured in an autobiographical statement by Schulz in 1923, occurred during a series of experiments performed more than four decades earlier. The seminal experiment involved the observation that low doses of chemical disinfectants enhanced the metabolism of yeasts while higher doses inhibited metabolism. Schulz said that the low-dose stimulation surprised him. In fact, initially he thought it was an experimental artifact and not a real, reproducible phenomenon. However, after numerous replications of the experiment, he became convinced that the phenomenon was real. He first presented these findings at a meeting about a year later for the local Medical Society.

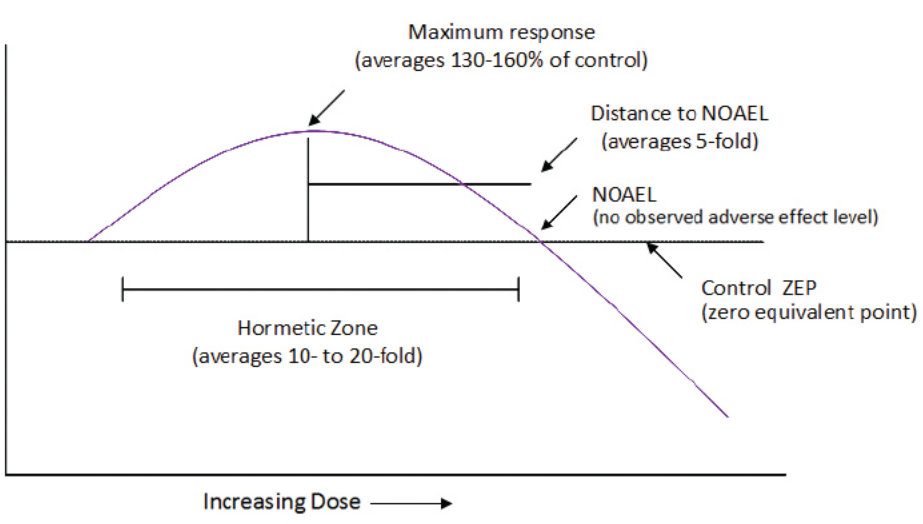

Figure 2
The Hormesis Dose-Response Model
The hormetic dose-response is biphasic in nature with a low-dose stimulation and a high-dose inhibition. The stimulatory response is typically modest in nature, being less than twice the control value in most incidences. The strong majority of the maximum stimulatory responses are only 30-60% greater than the control value. The width of the stimulatory response is typically in the 10 to 20-fold range. For approximately 5-10% of the hormetic dose-responses, the width of the stimulatory response is greater than 100-fold, sometimes exceeding 1,000-fold. The low-dose stimulation can display either desirable responses (i.e., increases in longevity, memory) or undesirable responses, such as enhanced growth of tumor cells in response to low doses of chemotherapeutic agents. In general, the hormetic stimulation should be seen as a highly conserved evolutionary trait that enhances the adaptive capacity to a broad range of toxic substances and stressor agents in the environment.

During the four decades preceding his 1923 report, four events occurred which were to give a new meaning to Schulz's observation and change the course of dose-response history—but not for the good.

Event (1): A clinical study in 1884 indicated that the homeopathic preparation veratrine was effective in the treatment of gastroenteritis.

Event (2): Research at Robert Koch's famous lab in Leipzig, Germany, discovered a bacterial cause of gastroenteritis and a method to culture it.

Event (3): Schulz conducted experiments to assess whether veratrine could kill the bacterial causative agent, and reported that veratrine was unable to kill the bacterium in *in vitro* culture studies, regardless of the dose.

Event (4): During discussions with his colleague Rudolph Arndt in 1885, Schulz connected his biphasic dose-response, discovered with yeast experiments, to the homeopathic study with veratrine and his own experiments which failed to find toxicity with this agent.

Schulz pieced the puzzle together this way: He claimed that the veratrine was effective in the treatment of the gastroenteritis despite its failure to kill the harmful bacteria. It worked, he said, by enhancing the adaptive capacity of the patient at low doses to resist the infection. He then linked this interpretation to his biphasic dose-response, concluding that homeopathic drugs act via the induction of adaptive processes at low doses, rather than any direct killing effect on the causative organism.

The Homeopathy Battle

Schulz generalized this explanation to the fields of therapeutics and toxicology, by providing what he believed to be the explanatory principle of homeopathy. Because traditional medicine was engaged in a highly acrimonious conflict with homeopathy during the 1880s and 1890s, Schulz literally gave homeopathy a major trophy: the biphasic dose-response.

These acts by Schulz led to his immediate rejection from the traditional medicine "club" and the label of traitor for the remainder of his life. It also created a new "context" in which traditional medicine could not view the biphasic dose-response concept objectively. Instead, the biphasic dose-response was marginalized and rejected, and traditional medicine replaced it with a model of its own making. Hence, the threshold dose-response concept was not only born out of personal experience and experimental findings, but also out of necessity; traditional medicine needed a dose-response model of its own.

The conflict between homeopathy and traditional medicine was complex, having philosophical, scientific, social, economic, and personalized elements, and so deep-seated that it has persisted for multiple generations. The hostilities enveloped and victimized Schulz and the dose-response concept, because Schulz had made the significant error of proclaiming that he had discovered the explanatory principle of homeopathy, basing it on his biphasic dose-response observations. By associating the biphasic dose-response model with homeopathy, Schulz never gave his new model the opportunity to be fairly considered by the proponents of traditional medicine. He placed it within a complex, long-standing, and bitter conflict.

Although the medical establishment and its scientific elite took aim at Schulz and his dose-response, this did not prevent other researchers from independently observing the same type of dose-response phenomenon. In fact, the occurrence of biphasic dose-response relationships, especially in the areas of plant biology, microbiology, and entomology, were common in the early decades of the 20th century, based on studies with chemicals and ionizing radiation (Calabrese and Baldwin 2000a-e). Despite such developments in the scientific domain, these findings were ignored or marginalized by the leaders of the medical and scientific establishment, who were interested in the destruction of homeopathy and its dose-response concept.

Eventually the medical establishment gained control of the funding, scientific literature, university curricula, and government regulatory programs—that is, the real power. By the mid-1930s, homeopathy was no longer a serious competitor and its biphasic dose-response was suffering a similar fate. Instead, the threshold model took center stage in the regulatory and academic toxicology arenas. Despite this major victory for traditional medicine, the establishment overlooked a very important feature of its new and successful dose-response model, which would eventually come back to challenge its scientific legitimacy: They neglected to validate the capacity of their model to make accurate predictions in the low-dose zone, that is, where people live. The medical/toxicological establishment never provided the proof that its model worked. The threshold model simply made untested predictions of responses based on studies with too few excessively high doses. This is what the fields of toxicology and risk assessment were—and still are—based on!

Why didn't the leadership of traditional medicine and their subsequent toxicological and risk assessment offspring ever validate the threshold dose-response model for low-dose zone responses? It would not have been a hard thing to do.

There is no definitive answer to this question in the scientific/medical literature. Perhaps no one in the "field" ever thought to do so; but could it have been simply overlooked and continued to be overlooked by so many practitioners for the entire 20th century? On the other hand, could it have been deliberately shunned over concerns of what to do if the threshold model did not perform as well as the biphasic dose-response model in head-to-head competition? The bottom line is that

Homeopathy and Hormesis

Hormesis is a dose-response relationship that is biphasic in nature. The low-dose stimulation occurs immediately below the toxic and pharmacological dose-response thresholds. In contrast, high-dilutional homeopathic practices as advocated by the founder of homeopathy, Samuel Hanneman, typically deal with exposures to therapeutic agents that are so diluted that there may not even be a single molecule within a treatment preparation. Thus, *there is no relationship between high-dilutional homeopathy and the concept of hormesis.* The two conceps became historically engaged when Hugo Schulz, the discoverer of the biphasic dose-response relationship today called hormesis, claimed that this dose-response could account for the therapeutic success seen in homeopathic preparations that were not highly diluted (i.e., those that had molecules in their treatment). Schulz was *not* a supporter of high-dilutional homeopathy. Hormesis is therefore a traditional pharmacological and toxicological concept and is not related in any way to high-dilutional homeopathy.

the issue of the experimental validation of the threshold model was not addressed until early into the new millennium.

Finally, Some Experimental Validation

In the first decade of the 21st century, our research group at the University of Massachusetts assessed the capacity of the threshold, linear, and hormetic (biphasic) dose-response models to make accurate predictions in the low-dose zone, using three separate and substantial data sets. In each case, the threshold and linear models performed very poorly, whereas the hormetic dose-response performed with a high level of accuracy. Thus, while it took nearly 70 years to vet out the dose-response model adopted by the regulatory communities, an answer finally emerged. It revealed that the models used by all regulatory agencies in the U.S. and elsewhere failed to make accurate predictions in the low-dose zone (Calabrese and Baldwin 2001, 2003; Calabrese et al., 2006, 2007, 2008, 2010).

Along a somewhat parallel track, but occurring in the 1950s, the threshold dose-response was challenged by the radiation genetics community, which argued that the effects of ionizing radiation on the genome were proportional to dose and that the nature of the dose-response was *linear*—not a threshold (Calabrese 2009b). This perspective was led by the Nobel Prize winner Hermann J. Muller who discovered that X-rays caused mutations in the germ cells of fruit flies. Muller apparently so feared the effects of radiation, that in his Nobel Prize acceptance speech, he deliberately deceived the audience.

In his Nobel Prize lecture, Muller stated that the dose-response for radiation-induced germ cell mutations was linear. He further emphasized that there was "no escape from the conclusion… there is no threshold." The problem for Muller is that only one month prior to his Nobel Prize lecture he acknowledged the results of a major new dose study from the University of Rochester supporting a threshold. In fact, Muller heaped praise for the quality of the study, noted its implications, recommended that it be repeated, all in a letter to the professor directing the study, Dr. Curt Stern. Such comments were contained and repeated in letters between Stern and Muller only five weeks before and after Stockholm.

Linear Overturns Threshold

After a prolonged effort that at times employed deliberately deceptive tactics by Muller and several colleagues (Calabrese 2011b,c; 2012a), the radiation geneticist community became a dominant influence, which took on major practical significance through the Biological Effects of Atomic Radiation (BEAR I) committee of the National Academy of Sciences. In 1956, this committee issued recommendations to the federal government that changed the course of risk assessment history. BEAR I argued that the assessment of mutation in germ cells by ionizing radiation should be considered as linear at low-dose. This judgment overturned the threshold model, at least in this one area. However, only one year later, the U.S. National Committee for Radiation Protection and Measurement (NCRPM) generalized this recommendation to somatic cells, thus including cancer. Many other governmental advisory groups across the globe joined in, and before long, linearity ruled the risk assessment world for cancer induced by ionizing radiation and chemical carcinogens (Calabrese 2009a), under the concept called Linear No-Threshold or LNT.

Throughout the first half of the 20th century there was little effort by those researching hormesis to summarize their collective findings and to offer a counter-position to the opponents of Schulz's biphasic dose-response. This is seen in a memorial article about the life of Schulz in the year after he died (Wels 1933). It was a reflection on how unfairly he was treated by his medical colleagues through techniques of professional isolation, marginalization, and intimidation. Such actions were not lost on Schulz's peers and were an effective means of keeping other potential dissenters obedient to the "company" line. One towed the line, or would face the same fate that Schulz long endured.

There was one major attempt to test the hormetic concept by a U.S. governmental agency in 1948. The U.S. Department of Agriculture (USDA), acting on numerous published articles reporting that low doses of radionuclides could enhance plant growth, put this concept to the test. In a large-scale but very poorly designed study, the USDA arranged for a 13-site assessment of 20 plant species (Alexander 1950). The subsequent failure of this study to support the hormetic dose-response hypothesis stymied a major opportunity for expansive testing, evaluation, and application of this concept. In retrospect, the USDA study was about as inadequate as could be imagined. There was no preliminary testing of the multiple plant species to estimate the threshold dose, all species were assumed to have the same hormetic zone, and most experiments used only a single dose. Any one of these deficiencies would have been catastrophic to the testing, let alone implementing the study with all three fundamental mistakes at the same time. In any case, this failure had profound implications for the hormesis concept to the USDA and agriculture, essentially killing it for the remainder of the century.

It is hard to understand how such poor study design decisions could have been made. It suggests either a profound ignorance of the hormesis phenomenon or perhaps a well-orchestrated attempt to see the concept fail the test.

Hormesis Emerges

The 1940s witnessed two important, but at the time, somewhat obscure developments, that would come to have important effects on the hormesis field. The first was that investigators at the University of Idaho observed the biphasic dose-response in experiments assessing the effect of extracts of the Red Cedar tree on fungal metabolism. These investigators, who were studying how fungi decay wood, called this phenomenon hormesis, for the Greek word meaning "to excite." These two researchers, John Erhlich and his graduate student Chester Southam, would go on to highly visible careers in the biomedical domain, leaving the concept of hormesis behind. Nonetheless, their terminology would stick, eventually replacing the Arndt-Schulz Law and Hueppe's Rule.

The second development was that a U.S. biochemist, Thomas Luckey, observed that low doses of antibiotics, in the absence of gut microflora, enhanced the growth of poultry. This unexpected finding eventually brought Luckey into the world of hormesis research. And 35 years later, Luckey wrote the first book on the subject, a major summary of ionizing radiation and hormesis (Luckey, 1980). Luckey had planned to develop a companion book on chemical hormesis, but that never happened. He did write an updated version of the ionizing radiation book a decade later (Luckey, 1990). However, it was his first book that had the most impact.

When Luckey's first book reached Dr. Sadao Hattori of the Japan Electric Power Research Institute (EPRI), Hattori became intrigued with the possibility that low doses of radiation could bring about positive health outcomes, perhaps even lowering cancer incidence, and he contacted the medical department of the U.S. EPRI. This connection set in motion a process that led to the first "Conference on Radiation Hormesis," held in Oakland, California, in August 14-16, 1985 (http://bit.ly/W935fs).[1] As a result of this conference, a series of activities was initiated that led to the current resurgence in hormesis by our group at the University of Massachusetts and others.

In parallel with the publication of Luckey's first book, there were independent developments by researchers in other fields who were starting to study the hormesis concept more systematically. For example, at the University of Edinburgh, Szabadi (1977) summarized the pharmacological literature concerning biphasic dose-responses and offered a mechanistic model to account for such responses. Likewise, epidemiological researchers started to publish findings on the occurrence of **U**-shaped dose-responses. Similarly, the neuroscience area reported a plethora of **U**-shaped dose-responses on numerous endpoints such as memory, anxiety, and pain (Calabrese 2008). And in the area of stress biology, the biphasic concepts of Robert Yerkes were transformed into a "Law" in 1957—the Yerkes-Dodson Law—which saw the biphasic dose-response as the basic feature of stress responses (Calabrese 2008).

These developments would be given an unexpected methodological boost from the debate over the desire to reduce the number of whole animals in toxicity testing and the desire to make greater use of cell lines. This transformation was a product of the 1980s, and it ushered in the testing of large numbers of agents over a far broader range of concentrations much more quickly, via high-throughput testing methods now so commonly employed. In fact, as a result of the transition to *in vitro* testing, the majority of published examples of hormesis over the past decade involve cellular systems.

That considerable growth has occurred with respect to hormesis is evident in the increased number of articles published on the topic, and citations of the articles within the leading professional scientific and biomedical indexes. For example, in the Web of Knowledge/Science database there were only 10 to 15 citations of hormesis per

Testing Which Model Gives the Most Correct Answers

The "big" model test experiments occurred using very large data sets that had thousands of different chemicals, tested over a large number of dose-responses in different biological organisms (i.e., bacteria, yeast, invertebrates, vertebrates, and plants). The data sets were subjected to *a priori* criteria so that they could be useful in assessing which dose-response model gave the most accurate predictions in the low dose zone, that is, the rules of evaluation were created before the assessments were conducted in order to prevent potential bias. The *a priori* entry criteria (i.e., which dose-responses were acceptable for evaluation) were such that each dose-response model would be treated equally and fairly so that no advantage was given to any dose-response model. In a similar fashion to the *a priori* entry criteria, separate evaluative criteria were also used for the evaluation of responses in the low dose zone. Based on the application of the evaluative criteria to all dose-responses satisfying the entry criteria, statistical judgments were made as to which dose-response model did best. In the three databases that our group studied, the hormetic model performed far better than the threshold and linear dose-response models, both of which performed poorly.

1. http://www.dose-response.org/low-dose/hormesis/pdf/Radiation_Hormesis_Conference_%28CA%29_April%201985.pdf

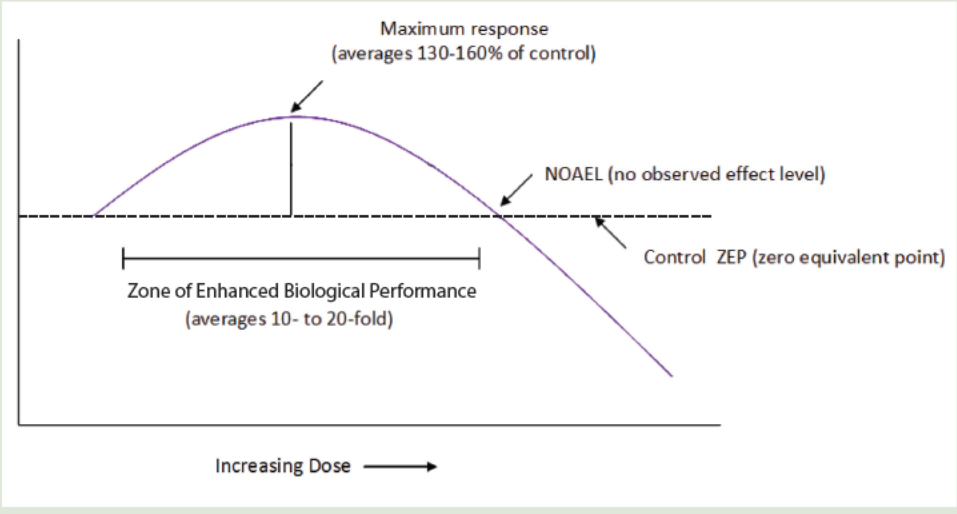

Figure 3
Dose-Response Curve Depicting the Quantitative Features of Hormesis and Its Application to the Concept of Enhanced Biological Performance

year in the decade of the 1980s. But in recent years, this number has exceeded 4,000 per year. Furthermore, it is possible that the number of authors and citations of the hormesis concept (rather than the term hormesis) is a substantial underestimate of the actual occurrence of hormetic dose-responses, because this phenomenon is often described by many other terms.

The Benefits of Hormesis

What emerged from these studies is the general and well-supported conclusion that hormesis is a real, reproducible biological dose-response phenomenon that is highly generalizable; that is, hormesis is independent of the biological model, endpoint measured, and chemical class or physical agent. It has very specific quantitative features, the most significant being that the magnitude of the stimulation is modest, usually less than twice that of the control group. In the majority of cases, the maximum stimulatory response is in the 130-160% range as compared to the control group response (i.e., 100%) (Calabrese and Blain 2005, 2009, 2011). The width of the stimulatory response zone is also generally modest, ranging 5- to 20-fold below the estimated threshold (Figure 3). However, about 5 to 10 percent of the examples of hormetic dose-responses displayed a stimulatory range greater than 100-fold, with some greater than 1,000-fold. These observations have important implications for the design of experimental studies, affecting the selection of the number of doses and sample size.

These quantitative features of the dose-response occur regardless of whether the stimulation is a result of a direct stimulus or an overcompensation stimulus. This suggests that the magnitude of the stimulatory response in this low-dose zone is not only independent of mechanism, but may represent a quantitative estimate of plasticity in biological systems. If this were the case, then it would indicate that the maximum pharmacological stimulatory response would likely be limited by the magnitude of the hormetic stimulation, having major implications for the pharmaceutical industry. In other words, increasing the dose of drug may not help the patient, if the maximum benefit is reached at a lower dose.

The low-dose stimulation represents a manifestation of biological performance within the constraints of plasticity, the limits of the organism's adaptability (Calabrese and Mattson 2011). It is therefore a highly regulated response, an integration of complex signaling pathway network mechanisms. These features of the low-dose stimulation are highly conserved, occurring from plants to microorganisms to man, and consistently seen across all affected endpoints (cancer and other diseases, for example) and at different levels of biological organization (cell, organ, organism).

The hormetic biphasic dose-response is now employed as the basis for numerous drugs. For example, pre-clinical data consistently show hormetic dose-response for anti-anxiety drugs, anti-seizure medications, osteoporosis prevention agents, Alzheimer's disease treatments, skin care products, and numerous other applications.

The Regulatory Challenge

Since the hormetic dose-response provides superior performance in low-dose predictions over that of the threshold and linear dose-response models, it challenges the use of those models by regulatory agencies. The failure of both threshold and linear models to pass multiple experimental validation tests, in contrast to the hormetic model, is an important finding. But despite the many reports of such findings in leading toxicological journals, regulatory agencies seem to show little institutional self-reflection or concern for the fact that the models they use for risk assessment and setting standards fail to accurately predict responses in the low-dose zone. It is difficult to imagine organizations that would continue to employ models that lack validation, and that fail experimental

validation when tested. This is especially the case when dealing with community exposure standards which have significant public health and economic implications. To take just one example: Many countries are spending billions of dollars to protect people from exposures to low radiation doses by setting extremely stringent standards, while creating profound fear of extremely low doses of radiation for which there is no demonstrable harm but in fact likely health benefits due to hormesis.

The hormesis concept addresses responses across the entire dose-response continuum. It has the capacity to detail both harm and benefit in the low-dose zone and it addresses the limitations of the threshold and linear models in risk assessment. By their strict adherence to the threshold and linear dose-response models, regulatory agencies can miss the possibility of either benefit or harm that occurs in the low dose zone. The use of the hormetic dose-response in risk assessment addresses these limitations of the threshold and linear models.

The EPA has further affected the public health by formally excluding the potential for benefit within the definition of a risk assessment. Denying a benefit is the equivalent of reducing the health status of the population (Calabrese 2011a). Congress created legislation that requires the EPA to protect the public from environmentally induced harm. In so doing, it is doubtful that Congress ever intended for their legislation to result in the denial of health benefits (Calabrese 2012b). By denying the possibility of health benefits from the definition of a risk assessment, the current EPA policy results in a higher incidence of environmental disease, higher medical costs, as well as higher regulatory costs for industry that are passed on to the consumer. This definition of risk assessment by EPA is incorrect scientifically and carries serious societal costs.

These failed environmental policies raise even more concern as they affect the risk communication message through the media and distort the education and research agenda. The EPA risk assessment process was wrong from the start. It was the product of an historical battle between homeopathy and medicine and the corrupted manipulation of the actions of leaders of the radiation genetics community, such as the Nobel Laureate Hermann J. Muller and his colleague Curt Stern.

It is time for society to be led by science, not ideology, in the matter of risk assessment. Society has suffered untold illness and incurred unnecessary costs in the process. It is time to reverse this process and choose low-dose exposure models based on experimental validation, rather than ideology.

Potential Benefits of Hormesis for Toxicology and Clinical Practices

Toxicology/Risk Assessment

Changes strategy for hazard assessment:

- Affects animal model and endpoint selection
- Changes the study design by altering the number of doses used, the range of doses studied, and the number of subject evaluated per dose

Changes biostatistical modeling:

- Predicts responses below background disease incidence, i.e., benefits

Improves risk assessment process:

- Refines and better targets uncertainty factor applications
- Differentiates benefits from harm below the toxicological threshold

Clinical Practices

Drug performance is constrained by the quantitative features of the hormetic dose-response.

High dose acting drugs may have different effect at low doses (i.e., anti-tumor drugs kill tumor cells at high doses but can stimulate proliferation at lower doses).

Clinical trial implications:

- Need to recognize interindividual variation in the hormetic dose-response
- Need to recognize the quantitative features of the hormetic dose-response
- Drugs can have multiple hormetic effects on different organs, creating a broad spectrum of beneficial and harmful effects.

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