Threshold — dose — response model — RIP: 1911 to 2006

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Summary

This essay represents a serious but fictional obituary of a scientific concept called the Threshold Dose–Response Model, which has long dominated the fields of toxicology and the broader biomedical sciences. Recent evidence indicates that the Threshold Dose–Response Model has long outlived its utility to predict low-dose effects. In fact, so poorly does this model predict low-dose responses that the idea arose that it should receive a symbolic burial recounting its achievements and failings, hence this obituary. *BioEssays* 29:686–688, 2007. © 2007 Wiley Periodicals, Inc.

Obituary

After a long illness the Threshold Dose–Response Model (called TM) died following a recent publication in Toxicological Sciences,[1] which determined that TM lacked the ability to predict responses in the low-dose zone. While the suddenness of the death came as a surprise to the toxicology community, TM had been ill for nearly a decade following the resurgence of the hormesis dose–response model (See Box 1), the success of which eventually weakened TM making it more susceptible to numerous challenges from researchers from the many disciplines interested in the dose–response, but especially those from pharmacology, radiation biology and toxicology. What tipped the scale and led to TM's final illness was a massive high-throughput study[1] with nearly 57,000 dose–response relationships in which TM was unable to predict the responses of 13 strains of yeast to 2,200 chemicals recorded in a US NCI database. Despite using a variety of techniques designed to solve the challenges presented by this database, TM just could not get a grip on the problem, failed to predict low-dose responses and simply stopped functioning, leading to clear signs of multisystem failure. Making matters worse and probably pushing TM over the top was that this challenge proved to be a snap for its hormetic rival.

The field of toxicology and others that have followed the battle for king of the dose–response in recent years knew the end was near for TM. In fact, on several occasions, TM had received the last rites of the Society of Toxicology and a prominent governmental agency, the US EPA, that had very heavily relied on TM since the Agency was created in 1970. These extraordinary attempts to revive TM by such prominent groups seemed to stabilize the hemorrhaging for a while, but the recoveries were temporary, relieving a few symptoms for a while, but never addressing the underlying causes of its terminal illness. While a high throughput dataset is listed as the official cause of TMs passing, the fact is that many other anticipated and equally stressful challenges would also have exposed TMs vulnerabilities and have been fatal as well.

In retrospect TM had a good run at it, leading the toxicology and pharmacology fields for nearly a century, fading into the historical archives after 95 years. TM, in fact, did not go easily into the stacks. It fought the upstart hormetic model on numerous occasions, data set by data set and, even though usually on the losing end of any comparison, still thought a full recovery may be possible, especially after the US National Academy of Sciences left the hormesis concept gasping for breath, even if unfairly, in the Appendix of the BIER VII Report.[2]

The problem with TM, but especially many of its followers, was that they thought the enemy was hormesis; they did everything possible to marginalize its significance and impact, often with such arrogant success that it acutely embarrassed the normally fair-minded TM. Yet history will likely tell that hormesis wasn't the enemy. Like the ancient Roman Empire, TM failed not because of external challenges (e.g. hormesis), strong as they were, but simply because of its own weaknesses and vulnerabilities.

TM was born, the creative expression of a pioneering toxicologist, in a basement laboratory believed to be without electricity. Even though documentation of the actual location and date of birth were lost due to archival damage from torrential flooding following the hurricane of September 1938 along the eastern seaboard of the US, converging evidence indicates that TM was kicking and screaming by late 1911. By the early 1920s, TM was beginning to make a reputation for itself based on unique achievements that applied powerful statistical principles to experimental toxicology and pharmacology; it also profited from the coordinated actions of some prominent pharmacological friends high up in the medical establishment in the early decades of the last century. These

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powerful friends undercut TM's main competition, a biphasic dose–response model (later to be called hormesis) that a German pharmacologist with strong homeopathic leanings was proclaiming.[3]

Early on, TM found a niche, particularly in the area of pesticide toxicology where it made remarkably accurate predictions. The toxicology world was astounded when the sigmoidally oriented TM not only predicted the amount of toxin that could cause 50% of a group of house flies and any other species to die but could do so with 95% confidence. Success lead to success and before long TM was used to predict risks from carcinogens. TM had a grip on all kinds of risks, from alcohol to X-rays and every type of toxic threat in between. TM became a real 20th century hero, saving countless lives from the ravages of chemical and radiation pollution and limiting the likelihood and seriousness of physician errors. TM was the man, I mean, Model. While a famous journal (i.e. Science) has named various chemicals "Molecule of the Year" during recent times, TM was much more than that. TM was "Model of the Century" and perhaps beyond or so most thought.

It wasn't that things were always easy for TM. In the 1950s a group of health physicists lost confidence, convincing their colleagues that TM just could not do the job of protecting against cancer risks from low doses of radiation. Some two decades later this criticism grew, infecting even old friends, like the US National Academy of Sciences and EPA, who joined the health physicists, no longer consulting TM for problems with chemical carcinogens. Although this hurt, TM took their abandonment with dignity, believing that "linearity at low dose" was toxicology's version of "political correctness" and that in time such prestigious groups would see the error of their ways.

Despite these setbacks, TM was not only respected but loved by all governments, cultures and ways of life. TM was always there to be helpful. TM was used by pharmaceutical companies to determine safe and effective dosages for people and pets, used by the government to help make the workplace safe, ensured that drinking water standards would actually protect people, was with the astronauts protecting them against exposures from outer space and from their spacesuits. TM even protected the children, before they became a political priority. Toxic wastes, no problem, TM was there to ensure that contaminated sites could be returned to a safe and useful setting. There really wasn't any one success that TM was most proud of, TM just liked being there in the middle of the action, solving problems, all kinds of problems.

About 20 years ago, the EPA went way overboard with its regulation of carcinogens, making cleanups excessively expensive, without being able to validate their always scary and often outrageous predictions of harm. This forced toxicologists to explore the finer details of the dose–response, something they had not done very well, probably because they all had so much confidence in TM, and why not! When one looks at a blade of grass from a distance it looks so nice and straight. However, a closer consideration reveals numerous irregularities, little holes and often some insect damage. Perfection vanishes under the microscope. So too with TM and the accuracy of its toxicological predictions.

That troublesome hormesis theory of the homeopathic leaning German pharmacologist had never really gone away. Somehow it was always there, far in the background, even though not taken seriously. Yet the hormesis dose–response idea became the vehicle to challenge EPA's strict cancer

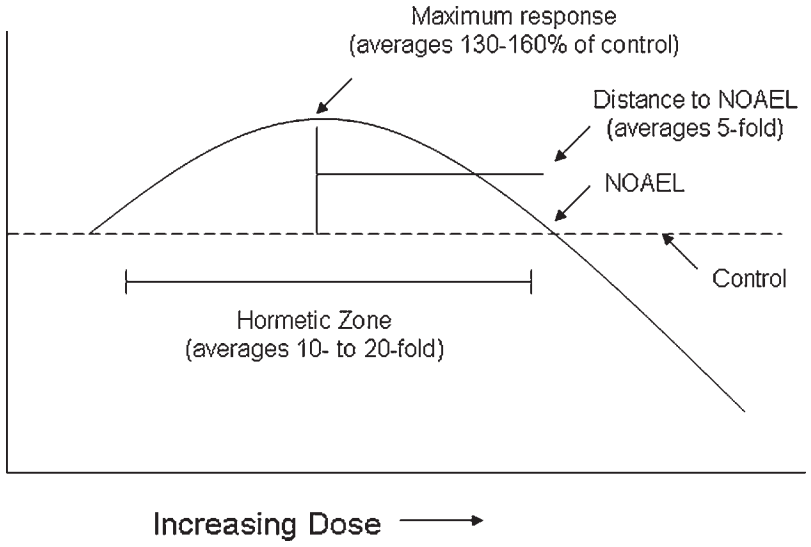

Figure 1. Dose–response curve depicting the quantitative features of hormesis.

Hormesis in a Box

Hormesis is a dose–response phenomenon characterized by low-dose stimulation and a high inhibition (Fig. 1). The term hormesis was coined in 1943 by Southam and Ehrlich[2] in research describing the effects of red cedar extractions on fungal metabolism. However, credit for discovery of the hormesis concept is typically given to Hugo Schulz at the University of Griswald in the late 1880s who assessed the effects of chemical disinfectants on yeast metabolism.[3] Hormesis, which is best evaluated in a dose–time–response framework, represents a modest overcompensation response following an initial disruption in homeostasis.[4,5] The low-dose stimulation is usually modest with maximum responses being only 30–60% greater than controls. The hormesis phenomenon is highly generalizable, being independent of biological model, endpoint measured, and chemical class/physical stressor agent.[6] Numerous mechanisms have been published that can account for specific hormetic dose responoses. Some general features of these mechanisms are now recognized. It has recently been proposed that concepts such as "preconditioning"/adaptive responses in the biomedical sciences, which typically protect organisms from toxic responses to subsequent and more massive exposures, are manifestations of hormesis.[7]

treatment regulation based on risk assessment and then basic dose–response understandings. In the intellectual battles that followed in which data were evaluated in model-to-model competition, TM (as well as its unverifiable "linearity at low dose" challenger) performed poorly—in fact, strikingly so. It kept losing ground, having to share more and more of its space in the classroom, at conferences, and in the major textbooks with hormesis. Old toxicological and pharmacological "friends" came to question TM's abilities in the low-dose prediction game, at first quietly and then more openly and embarassingly. As more massive amounts of data came in, it became clear that TM was actually like that blade of grass, with more imperfections than either TM or its followers would ever care to admit. TM's passing was peaceful, going out with the respect it earned and deserved. TM had privately confided to friends that, when the end comes, it should be at the hands of a strong database, a detailed analysis, rigorous peer-review and in a leading journal. TM got its wish.

So today we both mourn and note the passing of TM, a model that long served humanity. Modern times found the Achilles heel, for TM could never really get a handle on low-dose effects.

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