Dose-Response, NOAELs and Hormesis

By Frank Schnell — January 22, 2016

In the 16th century, Paracelsus, the Father of Toxicology, established that All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.

The truth of this 500-year-old statement should be intuitively obvious to anyone who has ever taken aspirin for a headache. If you take too little, you will get no relief; if you take the right amount, your headache will go away; and, if you take too much, your ears will ring and your stomach will hurt. Thus, dose alone determines whether a substance (aspirin in this example) will have an adverse effect (a poison), a beneficial effect (a remedy), or no effect at all.

One could describe most modern medications as judiciously applied poisons.

I. Dose-Response & NOAELs:

Most biological effects, whether adverse or not, are the consequence of a cascade of biochemical reactions initiated when chemical agents (referred to by pharmacologists and toxicologists generically as effectors, agonists or ligands) bind to effect-specific macromolecular receptors usually distributed on cell surfaces. It is of supreme indifference to the receptor whether the chemical binding to it is of natural, synthetic, endogenous, or exogenous origin. As long as the ligand fits into the receptor’s active site, the former will produce the effect mediated by that receptor.

This receptor-mediated mechanism of action accounts for the existence of thresholds of effect and for the S-shaped Dose-Response (D-R) Curve that typically results when the strength of the effect (from zero- to 100%-response) is plotted on the ordinate (y-axis) against the logarithm of the dose on the abscissa (x-axis) (Figure 1).
A sub-threshold concentration of the effector will not activate enough receptors to produce in the cell a significant effect. (If this were not the case, the effective regulation of normal metabolic processes would not be possible.)

These relatively ineffective doses are represented by the relatively flat, low-dose region of the D-R curve. Above that threshold dose or NOAEL (which will vary with endpoint and species), the elicited effect becomes significant and increases rapidly with increasing dose, as the ligand activates more and more of the available receptors. This is represented by the nearly linear, climbing, central portion of the D-R curve. Finally, when all of the available receptors are occupied by the ligand (i.e., saturated), a maximal effect is induced which is represented by the relatively flat, high-dose portion of the D-R Curve.

Depending upon dose, toxic exposures can produce a variety of adverse endpoints, ranging from temporary discomfort to death. The highest dose known NOT to cause a particular adverse effect is termed a No-Adverse-Effect-Level or NOAEL. Government agencies like OSHA, FDA, EPA, and ATSDR are able to establish safe levels of exposure to potentially toxic substances by simply dividing the NOAEL for the endpoint of interest by a chosen safety factor, which is typically one or more orders of magnitude (i.e., factors of ten). Safety factors are necessary because almost all NOAEls are established in laboratory animals, rather than in humans, and because significant biological variability occurs in all species. That having been said, political considerations typically prompt the selection of safety factors that are much larger than the facts alone would require, resulting in redundantly conservative (i.e., unnecessarily small) levels of safe exposure. For the same reason, safety factors for the same exposure may vary substantially between agencies with different missions.
For the last 40 years or so, the scare tactics of environmental extremists have successfully trumped the common sense of most citizens who have little or no scientific background, including even most of those who routinely take aspirin for their headaches. In particular, many people have bought into the invalid dichotomous argument that there are only toxins and non-toxins,” and never the twain shall meet. This distressing fact was most emphatically brought home to me many years ago, when I was the ATSDR toxicologist assigned to investigate water pollution at a trailer park in Louisiana. There, the drinking water had been contaminated with levels of vinyl chloride which, though harmless, were elevated by regulatory standards. And, there, a community leader who was posturing for the TV cameras at the time loudly proclaimed to me that [w]ether it s a teaspoon, a table spoon, or a cooking spoon, it s still poison.

Still, Paracelsus maxim (commonly abbreviated as The Dose Makes the Poison) remained a thorn in the side of environmental activists who, in order to fill their coffers and stay in business, need to keep the fear alive, in spite of the increasingly cleaner environments produced by increasingly strict environmental regulations. They therefore welcomed enthusiastically the public policy of zero-threshold for radiation and chemical carcinogens which took shape during the 1950s and 1960s. However, what they really wanted, and continue to push for, today, is an extension of the zero-threshold policy for carcinogens that would cover non-carcinogens, as well.

The facts, however, would lead us in the opposite direction, because radiation and chemical carcinogens, like non-carcinogens, have long been known to exhibit thresholds, too (Figure 2 and 3).
In addition to demonstrating that ionizing radiation-induced leukemia has a NOAEL around 0.15 Sieverts, Figure 2 also shows that, below the NOAEL, exposures above background apparently protect against leukemia, resulting in fewer cases than occur with normal background radiation (0.003 0.006 Sieverts per year; Relative Risk 1.0).

This is hormesis.
As shown by the 1943 data plotted in Figure 3, the demonstration of thresholds for chemical carcinogens predates the USEPA’s zero-threshold policies by more than a decade. Undaunted, environmental activists have insisted for decades that it was only the limitations of analytical technology that prevented us from seeing the frightening (but invisible) low-dose effects that they knew in their hearts must be there.

In a popular 1996 book, *Our Stolen Future*, Theo Colburn and her two co-authors created the notion that so-called environmental endocrine disrupters (e.g., phytoestrogens and other chemicals) which, in high doses, exhibited modest estrogenic or androgenic effects in humans, could produce severe hormonally mediated effects, including reproductive cancers, at the vanishingly small doses which prevailed in the general environment, even though the same severe effects were not seen at higher doses. In these circumstances, Colburn et al’s low-dose theory has been widely discredited among scientists without conflicting, activist agendas.

Because of regulatory considerations, most dose-response studies focused on adverse effects (and still do), and the investigators generally did not bother to look for any effects at all well below established NOAELs. Thus, many scientifically-challenged politicians in Congress assumed (incorrectly, of course) that anything was possible in this (presumably) unexplored no man’s land of the Dose-Response Curve, and immediately passed laws requiring EPA to take the issue seriously.

Thus, magical thinking became Law.

In fact, however, this region of the dose-response curve had not gone altogether unexplored. Many years before Colborn et al. had invented the spurious notion of low-dose [adverse] effects, several scientists had already taken a closer look at the very low dose region of the dose-response curve, in order to evaluate the scientific validity of the official zero-threshold policies of government agencies. (The limitations of experimental & analytical methodologies of the 50s and 60s...
What those scientists found was not altogether unexpected by the scientists, themselves, but it was a nightmare come true for environmental alarmists. To environmentalist alarmists devoted to keeping the fear alive, the only thing worse than a proven biological limit to the potential toxicity of a chemical (i.e., the NOAEL), would be the specter of actual beneficial effects at very low doses of that potential toxin. But, that is precisely what they are now confronted with in the well-established concept of Hormesis.

II. Hormesis:

_Hormesis_ is a biological phenomenon whereby a beneficial effect (improved health, stress tolerance, growth, longevity, etc.) results from exposure to very low doses of an agent that can be toxic, or even lethal, at much higher doses. Apparently, the concept is ancient, at least in principle, for Mithradates VI Eupator of Pontus (134 to 63 BC) is alleged to have regularly dosed himself with a cocktail containing low doses of 65 ingredients, as an antidote to poisoning.

Toward the end of the last century, Edward Calabrese rescued the hormesis concept from its abuse by homeopathy enthusiasts in the early 1900s and gave it a respectable foundation in the science of toxicology. Evidence for horometric effects has now been detected in virtually all toxicological studies which have included sufficiently low doses. But, most people are still unaware of the phenomenon.

During August, 1999, I co-taught the Basic Principles of Toxicology section of an Environmental Public Health Training Module for Health Assessors at the Agency for Toxic Substances & Disease Registry (ATSDR). As a concluding exercise, I had the students plot a dose response curve using four actual data points for excess frequency of turbinate carcinomas in female rats treated with dioxin for 2 years in the classic chronic bioassay by Kociba et al., 1978 (Figure 4).
I kept the identity of the test agent a secret until the end of the exercise, because I had a surprise in store for the students. They were all aware that ATSDR and EPA policy dictated that dioxin (2,3,7,8-tetrachlorodibenzodioxin) was the most potent zero-threshold carcinogen known to man. The EPA had even declared TCDD to be a known human carcinogen in 2000, in spite of the absence of epidemiological evidence to support such a claim. (The US EPA had actually rewritten its Cancer Risk Assessment Guidelines (CRAGs) to allow itself to label TCDD as a Known Human Carcinogens, without the epidemiological data that previous CRAGs had required in order to demonstrate a cause & effect relationship.)

Almost none of those health assessors had ever heard of the concept of Hormesis. But, by the end of the class, they knew that, over 20 years earlier, there had been actual data available demonstrating not only that the concentrations of TCDD present in the general environment were not carcinogenic, but that the anti-carcinogenic properties of dioxin far exceeded its carcinogenicity at doses much higher than humans could normally encounter.

In fact, at the 49th Annual Meeting of the Society of Toxicology in Salt Lake City (2010), scientists reported evidence that binding of AhR agonists (including dioxin and dioxin-like compounds) to the Aryl Hydrocarbon Receptor (AhR), caused a reduction of cell proliferation in human breast cancer cells, suggesting that AhR agonists might someday be used in the treatment of breast cancer. This is particularly ironic, because EPA had long used binding to the AhR as a surrogate for toxicity to develop so-called toxicity equivalence factors (TEFs) for dioxins, PCBs, and other dioxin-like compounds.

The hormesis model of dose response is vigorously opposed by those who would deny the
concept has any relevance at all to the risk assessment and regulation and of environmental chemicals. This opposition does not derive from any lack of evidence for this well-established toxicological phenomenon. Rather, it follows from the historical animosity that environmental alarmists have for any scientific fact (including the threshold concept) that would limit their ability to frighten people with specious claims that so-called toxins in the environment can produce serious adverse health effects, regardless of concentration.

Actually, hormesis is much more relevant to the risk assessment and regulation of chemicals in the environment than one might think.

Because the maximum hormetic effect (about 30-60 percent over controls) usually occurs 4-5-fold below the NOAEL for a particular chemical and endpoint, the 10-10,000-fold safety factors currently employed by such agencies as EPA, ATSDR, and FDA are often protecting us all from the low-dose beneficial effects of chemical exposures, as well as from the potential high-dose toxicity of the same substances (Figure 5).

![Hormesis - Dipping into the "Beneficial Zone"](image)

Figure 5.

While the biochemical mechanisms by which hormesis works have not yet been conclusively established, it is logical to expect that the same defense and repair mechanisms that are activated by low doses of a given toxin or other stressor, in addition to preventing any significant damage by that specific toxin/stressor, would also have an ameliorative effect on any other related damage, regardless of cause, thereby exerting a generalized beneficial effect.

Even without environmental activists promoting Chicken Little toxicology, the hormesis concept still might not be as well-known as it should be. This is because the subject is, in my opinion, unnecessarily obfuscated for the uninitiated by the same specialized jargon and methodologies that all professionals use to mystify their discipline and distinguish it from all others. In the case of hormesis investigators, that meant inverting the hormetric dip in the low-dose region of the standard dose-response curve (Figure 6), and labeling the beneficial effect (which is now above...
the zero-effect line on the X-axis) as stimulation," and labeling the adverse effect (which is now below the zero-effect line on the X-axis) as inhibition (Figure 5 and 7).

Thus, what could have been more simply represented in the low-dose region of familiar dose-response curves was represented instead by members of the new sub-discipline in an unnecessarily esoteric fashion.

Epilogue:
As a board-certified, PhD toxicologist (retired), I would much prefer that the Hormesis Concept had
been de-mystified and made abundantly clear to the general public which has, for far too long now, been deceived by the scientifically bankrupt scare tactics of unprincipled people with political agendas.

These deceptions were bad enough when they were just being used to spread irrational fears about industrial pollutants in the environment. But now, with ever-increasing intensity (or hysteria), they threaten the very survival of modern civilization, by diverting much needed funds from the solution of very real problems, at the very time when the world’s economy is already hanging by a thread.

In my opinion, it rises to manipulation of a vulnerable public so dire as to be construed as borderline criminal to spread irrational chemophobia that makes a young mother afraid to breastfeed her baby or feed fish to her family.

Of course, this too shall pass, someday. But, we cannot afford to wait for divine intervention. Instead, we must all learn to answer the Serenity Prayer for ourselves. Because, in an Age of Political Correctness Gone Mad, only the well-informed will retain their sanity.

Note: The Serenity Prayer is:

"God grant us the serenity to accept the things we cannot change, the courage to change the things we can, and the wisdom to know the difference."

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