Toxicology rethinks its central belief

Hormesis demands a reappraisal of the way risks are assessed.

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How clean is clean? Billion-dollar arguments on this question are common in the United States, as agencies — such as the Environmental Protection Agency (EPA) — face the need to remediate sites of uncontrolled or abandoned hazardous waste, Ground Zero being the foremost example in many minds. Likewise, debates rage about 'safe' levels of compounds in the body, for example lead-associated cognitive deficits in children, which are claimed to occur at blood lead levels lower than previously thought. In addition, the US Congress is exploring whether low doses of organic mercury preservatives are contributing to an apparent marked increase in childhood autism.

These, and numerous other examples, illustrate the central role that toxicology and the knowledge of the dose–response relationship play in a vast array of critical environmental, medical and public-health issues. As regulatory and public-health agencies base their decisions and policies on toxicological predictions, they are therefore of considerable importance to vast numbers of people as well as to national economies.

We believe the predictive models that all regulatory agencies use are based on a fallacy in the toxicological models used to predict and extrapolate dose responses from chemicals, pharmaceuticals and physical stressor agents. Here, we clarify the basis of this fallacy and advocate a more predictive model that will revolutionize public attitudes towards risk.

Traditional models

The most fundamental concept used in toxicology to determine risk assessment and regulation is the dose-response relationship, for which two models have traditionally been used. The threshold model (Fig. 1a) is used in the assessment of risks for non-carcinogens, and the linear non-threshold (LNT) model (Fig. 1b) to extrapolate risks to very low doses of carcinogens. But we believe the most fundamental shape of the dose response is neither threshold nor linear, but U-shaped (Fig. 1c), and hence both current models, especially the linearity model, provide less reliable estimates of low-dose risk.

This U-shape is commonly called hormesis — where a modest stimulation of response occurs at low doses and an inhibition of response occurs at high ones[1]. The stimulation is often (but not always) observed following an initial inhibitory response, appearing to represent a modest overcompensation to a disruption in homeostasis[2]. Depending on the endpoint that is measured, the hormetic dose response is either an inverted U — the endpoints being growth (such as the effects of low doses of various toxic metals, herbicides and radiation on plant growth) or survival (such as the effects of low doses of gamma rays on longevity in rodents) — or a J — the endpoint is the incidence of disease (for example, mutation, birth defects, cancer; Fig. 1c). Yet virtually all the leading toxicology textbooks consider only the traditional threshold and linear models.

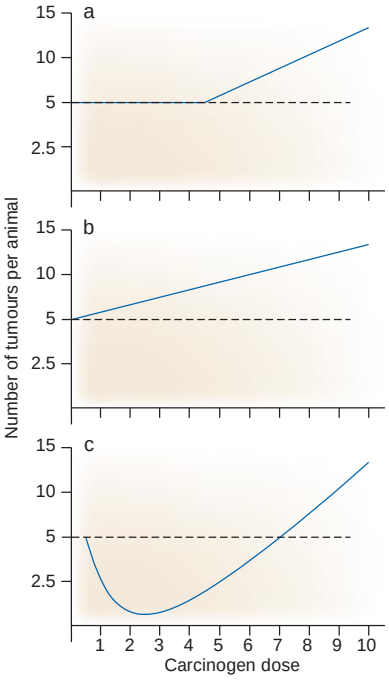

Figure 1 **Hypothetical curves depicting (a) threshold, (b) linear non-threshold, and (c) hormetic dose-response models using cancer (number of tumours per animal) as the endpoint. The reduction in number of tumours per animal at the lower doses (1–6) compared to the number of tumours per animal (5 tumours per animal) in the control indicates a reduced risk of cancer.**

The toxicological community made an error of historic proportions in its formative years (the 1930–40s) in buying into the threshold model[3]. Once accepted, this model became dogma, providing the basis for subsequent progress and confusion — despite toxicologists, radiation biologists, pharmacologists and others regularly pointing out unmistakable exceptions to the so-called threshold rule, such as the effects of saccharin, dioxins, cadmium, mercury, numerous insecticides/herbicides, and numerous pharmaceutical agents. These unexpected results were generally written off either as reproducible but 'paradoxical' phenomena with no apparent capacity for generalization, or as biologically irrelevant random variation.

The implications of this systematic error are immense, not least in toxicological risk assessment. The *a priori* criteria we developed to assess whether experiments displayed evidence of hormesis based on study design, magnitude of the stimulatory response, statistical significance of the stimulatory response and reproducibility of findings, revealed up to 5,000 examples of hormetic responses independent of chemical class/physical agent, biological model and endpoint measured. Low levels of agents such as cadmium, dioxin, saccharin, various polycyclic aromatic hydrocarbons, X-rays and various gamma-ray sources reduce tumours in some species. Low doses of X-rays enhance life span in male and female mice and guinea pigs; ethanol and acetaldehyde enhance longevity in fruit flies; multiple stressor agents extend longevity in nematodes; numerous toxic substances (for example, cadmium and lead) enhance growth in various plant species. Low or modest consumption of ethanol reduces total mortality in humans, while increasing it at higher levels of consumption. The hormesis concept is thus highly generalizable and far-reaching.

Yet the vast majority of toxicological experiments are not designed to evaluate the hormetic hypothesis, assessing doses that are too high for the hormetic domain. Of those experiments that do have adequate study designs, a substantial proportion demonstrates hormesis. Using a database with rigorous and clearly defined entry and evaluative criteria, the hormetic model strikingly outperforms the 'dominant' threshold model[4]. The hormetic model is not an exception to the rule — it is the rule.

Overlooking hormesis

So how did the field of toxicology get its most fundamental tenet, the nature of the dose response, so wrong? One reason is that, as mentioned above, most toxicological experiments lack the capacity to assess possible hormetic dose responses. Yet even when they do have potentially adequate study designs, the hormetic response can still be missed because at the assumed toxicological threshold dose (called NOAEL, for no observed adverse effect level), there is often evidence

of a low degree of toxicity, even if the response is not significantly different from the control group. As the dose below the standard threshold becomes progressively more dilute, the response becomes more likely to exceed the control value (hormetic-like). This is why mammalian toxicological studies, which emphasize high-dose toxicological responses such as those used to assess possible carcinogens in the US National Toxicology Program (NTP), are often incapable of adequately assessing the hormetic phenomenon. We believe that this combination of circumstances contributed significantly to the toxicological community overlooking the hormetic model and putting full emphasis on the threshold model for non-carcinogens and the linear model for carcinogens.

The mechanism by which hormesis occurs has also hindered its general acceptance. Toxicological researchers have rarely focused on why there are transitions (for example, stimulation followed by inhibition) in dose responses. Molecular pharmacologists, on the other hand, have focused on how such switching mechanisms work and how they affect the nature of the dose response, including hormetic-like biphasic dose–response relationships. There are more than 30 pharmacological receptor systems in the published literature that affect hormetic-like dose responses where the mechanisms that account for such responses have been clarified to at least receptor level[5]. These findings reveal that there is no single hormetic mechanism, but suggest a general strategy for resource conservation across biological systems.

Seven years ago, hormesis would not find its way into even informal conversation among toxicologists. Now, we not only know that it exists but accept its dominance over other models. The implications are enormous: they affect how toxicologists select biological models, choose endpoints to measure, design studies, assess risk and even pose the questions and the hypotheses they test. The dose response affects nearly all aspects of toxicological, pharmacological, epidemiological and clinical evaluation.

Implications of hormesis

What are the implications of the hormetic perspective? Most notably, it challenges the belief and use of low-dose linearity in estimating cancer risks, and emphasizes that there are thresholds for carcinogens. The economic implications of this conclusion are substantial. The EPA has been struggling to harmonize how it assesses risks from non-carcinogens and carcinogens, having mistakenly assumed for a long time that non-carcinogens act via a threshold model whereas carcinogens act via a linear model at low doses. As both types of biological response follow the hormetic paradigm and display similar quantitative features of the dose response, the EPA could use the hormetic model as default to assess risk in both non-carcinogens and carcinogens[6].

Hormetic responses have equal, if not greater importance, for the biomedical and clinical sciences

The hormetic perspective also turns upside down the strategies and tactics used for risk communication of toxic substances for the public[7]. For the past 30 years, regulatory and/or public-health agencies in many countries have 'educated' — and in the process frightened — the public to expect that there may be no safe exposure level to many toxic agents, especially carcinogens such as radiation and dioxins. If the hormetic perspective were accepted, the risk-assessment message would have to change completely. Changing a dominant risk-communication paradigm is not as simple as flicking on a light switch. It changes beliefs, attitudes, and assumptions, not unlike changing from a Soviet-style society to a western one. It would certainly be resisted by many regulatory and public-health agencies as an industrial-influenced, self-serving scheme that could lead to less costly, less protective clean-up standards, reminiscent of attempts by early opponents of hormesis to link it with homeopathy.

Hormetic responses have equal, if not greater, importance for the biomedical and clinical sciences. Many antibiotics, antiviral and anti-tumour agents, and numerous other medicines display hormetic-like biphasic dose responses: one dose may be effective clinically but another may be harmful. Some anti-tumour agents (for example, suramin) that inhibit cell proliferation at high doses, where they may be clinically effective, become like a partial agonist at lower doses, where they enhance cell proliferation. This is also true for some antibacterials (erythromycin and streptomycin, for example) and antiviral agents (such as gliotoxin analogues, colanolides, adefovir and Rhamnan sulphate). In these cases, the drug may be harmful to the patient at lower than therapeutic doses and requires careful clinical supervision. Some Alzhiemer's treatments, such as the second/third-generation anticholinesterase agents, often enhance cognitive function at low doses but decrease it at higher doses. Thus, the hormetic biphasic dose response provides not only new opportunities for clinical improvements but also risks that have to be addressed.

Exercise is now being seen as a similar phenomenon, in that there may be an optimized degree of exercise that confers a wide range of benefits, whereas at higher levels (dose), the net result would be adverse. Immunology is likewise replete with examples of both chemical- and radiation-induced hormetic-like biphasic dose responses for a broad spectrum of endpoints and biological models. More than 150 endogenous agonists, drugs and pollutants induce hormetic effects in humans and other animals, affecting antibody production, cell migration, phagocytosis of microbes, destruction of tumour cells and other end-points. A better understanding of such phenomenon would have important implications for future research and biomedical development.

Paradigm shift

At a time when the human genome has dominated many aspects of the scientific literature, it is generally unrecognized that the dose response of most, if not all, peptides conform to the hormetic model. Recognition of hormetic-like biphasic dose responses is important for elucidating the bioregulatory actions of various peptides and their biomedical implications.

Yet hormesis is not easy to study, as it requires the use of more doses (especially in the low-dose zone), often including a temporal component (measurement at various times within an experiment) and using more subjects to enhance statistical power, and needs replication. These extra features often steer researchers to less resource-intensive and more readily definable phenomena.

The hormetic dose response represents a paradigm shift in the concept of the dose response throughout biological science. It is widespread and outperforms other dose-response models. A general recognition of the hormetic perspective is likely to yield a vastly improved evolutionary basis of adaptive responses, scientific foundations of risk assessment and clinical medicine, as well as a more biologically plausible framework for understanding regulatory strategies at the level of the cell and the organism. ■

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