CHANGING CHALLENGES AND PARADIGMS

Donald E. Stevenson, Ph.D.
Austin, TX 78738
E-mail: dsteve65@aol.com

ABSTRACT

Change comes as a surprise because things do not happen in a straight line. Concepts often evolve haphazardly, reacting to specific events. Assumptions are made but are not challenged, sometimes for political or social expedience. It has long been recognized that the dose makes the poison. Concepts of the relationship evolved from both events and the availability of exploratory tools. There are consequences to risk aversion. The general concept of Hormesis is perhaps not unexpected. The acceptance of multiphasic dose-responses has the potential to unleash additional and productive insights into this relationship. The activities of BELLE and it's Newsletter provide an excellent example of what can be achieved when dogmas are challenged by the accrual of information that has not been previously examined to see whether additional insights are possible. A forthcoming challenge will be the critical examination of all the inputs and assumptions that will be used in the increasing sophistication of biological modeling.

Key Words: hormesis, hormetic, biphasic, risk assessment

THE WORLD IS DIVIDED INTO PEOPLE WHO THINK THEY ARE RIGHT (ANON)

Fifty years ago I was researching some effects of agents used in anesthesia where the 'dose' was what was put in the syringe and the effect was assessed directly on the subject. Consumer toxicology was in it's infancy, evolving from pharmacology and emphasizing doses that were without measurable effect (or adverse effect). There was no Society of Toxicology or other group interested in risk assessment. The FDA had issued the 'Gray Book' – less than half an inch thick – describing the appraisal of chemicals and drugs. About fifteen years earlier two compounds emerged that saved many millions of lives prior to their potential effects being fully investigated. Indeed, a lengthy regulatory process at that time would have led to millions of deaths. Penicillin had defied the efforts of Florey and Chain to produce testable amounts until finally there was sufficient for injection into a single mouse by John Barnes (later head of the MRC Toxicology Unit). The mouse survived and soon there were sufficient amounts to treat a few individuals with life-threatening infections. Penicillin became a key element in reducing deaths from wounds in World War Two.[1] The other compound that saved many millions of lives is DDT. Again, the first large 'toxicology' experiment involved the application to American troops in Italy facing an outbreak of typhus. Malaria was also a major source of morbidity and mortality in the Pacific zone. After the war, the potential for DDT to control mosquitoes and malaria was exploited by U.S. Public Health authorities. Malaria was still endemic in the U.S.A., particularly in the Mississippi basin.[2] Toxicology was being driven by pragmatic responses to major health issues. Thalidomide slipped through the net. There was not a comprehensive requirement for examining reproductive endpoints in many countries. The use of statistics in experiments and epidemiology was also not universal. The 1956 landmark paper of Sir Richard Doll and Bradford Hill concerning smoking was a major turning point for human disease investigations.[3]

The comprehensive testing of chemicals for carcinogenicity was not yet a requirement by the FDA. However, by the late fifties the FDA showed in two year studies with comparatively small groups of animals that DDT might induce liver tumors. Public opinion was galvanized by Rachel Carson and was one of the factors leading to the formation of the U.S. Environmental Protection Agency. The other, often unrecognized, event was the 1960 recommendation by James Lovelock the eminent scientist and environmentalist ('Gaia') to Lord Rothschild, then head of Research in Royal Dutch/Shell that an electronic capture detector device that he had developed, coupled with gas-liquid chromatography would be a significant advance in the measurement of organochlorine compounds.[4] Overnight the limits of detection were lowered by 2-3 orders of magnitude and 'no-residue' applications suddenly gave measurable residues and evidence of environmental contamination. Regulatory agencies were now confronted with the need to make judgments on the safety of these residues.

One of the first actions of the Environmental Protection Agency was to seek the cessation of the use of DDT and dieldrin. While the focus on DDT related to environmental effects, the Agency, together with the Environmental Defense Fund moved from Cancellation Hearings to Suspension Hearings on dieldrin that could be rapidly completed. A key issue was how to determine an acceptable intake for a compound that caused tumors in animals. Mantel proposed a linear model that utilized a probit unit per log increment in dose. He concluded that this was sufficiently conservative to include all the dose-response data that was then available. The concept of linearity was subsequently developed by Kenny Crump and others into the linearized multistage model that has dominated toxicological dogma for the last three decades. While linearity was initially considered for carcinogens, it spread to other endpoints. There remains a regulatory dichotomy. The EPA has regarded liver tumors as indicative of probable human carcinogenicity, whereas the FDA allows the sale of several classes of very widely used drugs that produce a similar response, sometimes in both rats and mice.

My initial interest in hormesis arose from articles by Harold Boxembaum and Pat Neafsay who utilized data from a large mouse study that we had conducted on dieldrin to demonstrate an apparent hormetic response (see ref 5). I was already interested in the literature on aging and the use of the Gompertz-Makeham (G-M) model

that was commonly utilized in that sphere and that had been used by Pat Neafsay. Following a presentation by Bob Sielkin to a group of epidemiologists it dawned on us that they and animal-based risk assessors used entirely different mathematical approaches due to the way data is developed. Bob proposed that in epidemiology every individual could be regarded as a unique dose group in terms of dose and time. He developed the approach to determine whether potential nonlinearities existed in the age or non-age component.[5] This allowed a more refined analysis of epidemiology information. One apparent reason for rejecting the widespread use of the Gompertz-Makeham model, apart from the fact that is nearly two centuries old, is that at extreme ages the data diverges from the model in that the annual mortality risk remains stable. However, at that stage the remaining population does not represent the attributes of the initial cohort, but rather a unique subset and the deviation actually provides valuable insights.

Modeling has now become part of our national life, driving the forecasting of every dimension of our future, including weather, global warming, economic and health trends. The use of sophisticated models only became practical with the advent of readily available electronic computing about thirty years ago. Among the advances has been the investigation of non-linear, self-organizing systems involving feedback mechanisms that are common in biology. Thus, it has become possible to explore the nature of multi-phasic dose-responses. On a cautionary note, I find that many papers now utilize statistical packages that may not be transparent, providing an illusion of a comprehensive analysis but lacking the thoughtful comprehension of the nature of the information being analyzed. Elsbeth McKay from Australia commented in the January 5th 2008 issue of the New Scientist 'automated thinking tools tend to block people's capacity to see or know the broader context of the problem they face'.

Our exploration of a variety of modeling issues coincided with the spear-heading of the concept of hormesis by Ed Calabrese. It soon became a natural union of interests. Initially the meetings that he organized might be characterized as the exploration of an interesting concept, but needing supporting data. Ed has remarked that "the concept of hormesis may invoke negative judgment by those involved with the practice of medicine as well as those involved with reducing exposures to harmful agents via regulatory activities."[6] The medical hesitancy was related to the possible confusion with homeopathy, while the hesitancy was shared with many in the environmental community who felt that any deviation from linearity was against an almost religious belief that any exposure was bad by definition. A senior member of the EPA Cancer Assessment Group once remarked to me that the Agency was not interested in chemicals that might reduce the risk of cancer. This is also reflected in the wording in the 1986 Guidelines concerning risk estimates that are unlikely to be greater than the upper bound estimate and may be as low as zero – with no acknowledgement of the possibility of less than zero.

Ralph Cook remarked 'We all perceive only what we expect to perceive".[7] His historical paper is worthy of review – he concluded that "The biological effects of the low-level exposures (BELLE) initiative does not dismiss findings that have already been obtained in valid biological research. It incorporates them, accepting the tested observations at high levels, but questions the assumptions related to low level exposures and offers alternative theory: low level exposures may produce paradoxical effects." The BELLE Newsletter provided an informal, readable and timely mechanism for publishing a variety of high quality papers covering a wide range of relevant issues.

A defining moment for BELLE was the support given from Dr Holland's Institute for the Advancement of Chemical Technology at Texas A & M University that allowed Ed with the support to conduct an extensive literature review to define the potential universality of the concept of hormesis. His exhaustive literature analysis revealed many examples in varied systems, suggesting that there is a phenomenon that should be considered in estimating dose-responses. It wad quickly realized that there are issues of measuring such effects in animal studies which have limited dose levels and numbers of subjects per dose.

What is truly remarkable is the emerging acceptance of non-linearity and multiphasic dose-responses. When Ed Calabrese began his journey I gave him a near zero chance of changing the opinions prevailing in the 70's and 80's. However, by his persistence, diligence and organizing abilities, Ed has enlarged the concepts of dose-response that in turn must be reflected by the evolution of the design of experiments. In the BELLE Newsletter and succeeding publications Ed has fostered the input from a wide variety of sources and has allowed a full and frank discussion of the issues. While each change may be incremental, over time progress has been dramatic. The long-term benefits to society may be great if a more flexible, but science-based understanding of risk estimates leads to a more focused reduction of risks.

My congratulations to the BELLE Newsletter and to Ed Calabrese as the instigator and editor.

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