

How much is Enough to Accept Hormesis as the Default?
or
“AT WHAT POINT, IF EVER, COULD/SHOULD HORMESIS BE EMPLOYED AS
THE PRINCIPAL DOSE RESPONSE DEFAULT ASSUMPTION
IN RISK ASSESSMENT?”

Michael A. Jayjock, PhD CIH

To consider where we want to be tomorrow my sense is that we first need to consider where we are today. In this treatment I will attempt to do this with the more general example of non-carcinogenic chemicals. The primary method of conducting toxicology today remains the testing of a relatively few animals at high dose for morphological or behavior changes. I have always found this to be a somewhat unrefined system fraught with uncertainty.

An important question becomes: How do we handle the intellectual insecurity of such issues as:

- animals as surrogates for humans,
- the testing of a relative few as representative for all and
- tested exposures that are typically orders of magnitude above those realistically anticipated in the real world ?

The short answer for me is that we manage this cloud of uncertainty by attempting to purposely overestimate the risk. I have heard a number of colleagues say “The purpose of a toxicity study is to find toxicity”. Thus, the toxicological doses are chosen to provide a ranges of adverse responses. Starting at the top with a frank untoward health effect in the test animal that then monotonically decreases with decreasing dose and finally results in a low-dose response that is indistinguishable from the untreated controls (this is the much sought after and somewhat variable No Observed Adverse Effect or NOAEL). Given the lack of confidence that results from the above uncertainty inducing elements of species, statistics and exposure level, the standard procedure with non-carcinogens is to divide the NOAEL by an expert-generated but somewhat subjective safety (SF) or uncertainty factor (UF) to arrive as an exposure level that is declared to be essentially “safe”.

Depending on the size of the SF or UF and the population at risk this “safe” exposure may or may not be forwarded as being protective of all persons exposed at or below that level. For example, in the case of the work place exposure limit forwarded by the American Conference of Industrial Hygienist, these levels are explicitly represented as being protective of “nearly all” workers exposed at these levels for a working lifetime.

Even though it may not be stated openly, from my perspective, the above appears to be based in the working hypothesis that non-carcinogens conform to a threshold model of toxicity and that the exposure limit is hopefully at or below the threshold for “nearly all” or everyone.

Looking at this current reality objectively, I have asked myself, “Is this the best that we can do?” Indeed, a few years ago Phil Lewis, Jerry Lynch and I wrote an opinion piece outlining an approach that would use the available data and mathematical modeling to ascribe the level of residual risk that might be extant at any exposure limit or other assigned “safe” level of exposure (Jayjock, Lynch and Lewis, 2001) . It was basically an attempt to deal with the same types of uncertainties as outlined above but to do so in a more quantitative, transparent and ostensibly less subjective manner. In the end, however, the same problem prevails regardless of the approach, ***the inherent quality of typical toxicological data are simply too poor to allow for an understanding of what really occurs in human tissues at the relatively low-doses generally extant in the environment.***

This is not to criticize the current system merely to explain its limitations. My sense is that it has served us well especially in the context of a quote I once heard from a famous leader whose name escapes me:

“Some questions can not be answered but they must be decided.”

I believe that for the most part the folks setting exposure limits using this methodology have done the best they could within the confines of the information and science. I believe it is, however, exactly this lack of available knowledge provided by the current paradigm that will keep hormesis from ever being used within it.

In short, I do not believe that we will ever be able to move off of the threshold hypothesis if we continue with the current toxicological testing paradigm and its concomitant lack of elucidation. I believe that a basic change in how we do toxicology is needed.

I agree that those who study hormesis are making an increasingly stronger case for it as a viable and perhaps preferable hypothesis. Recent findings do indeed suggest that the data underlying the theory are convincing and that hormesis is not only highly generalizable across biological systems, toxicological end-points and chemical class, with mechanistic understanding, but also more dominant in nature than other dose-response models including the threshold model.

I agree with the mounting evidence; and I believe that hormesis should be the hypothesis of choice in risk assessment. But what might this mean in practical terms? One obvious and expensive possibility would be to conduct toxicology testing in a manner similar to the current practice but to shift the emphasis to low-dose response. That is, establish the toxic end-point with a few animals at high dose and dedicate the remaining resources to elucidating a NOAEL and looking for signs of stimulation at a reasonable fraction of the NOAEL. I believe that this would clearly be more expensive but it is at least potentially doable and could provide direct evidence of hormesis for that class of compounds.

The truth is that I honestly do not think that the “more of the same” approach described in the above paragraph would be a cost-effective line of attack. Nor do I think it will happen. My sense is that we simply need to be able to look much more deeply into the “black box” of human tissue response to chemical exposure and to do this we need to develop or otherwise exploit the new tools of molecular biology.

So my answer to the question posed for this piece is that ***we will only be able to move forward with hormesis as a default hypothesis after the development and use of tools from the realm of molecular biology.*** I offer this as someone with a professional background long in engineering and short in biology. Hopefully, my lack of specific knowledge in this area will not be too damaging to the credibility of the message or to the potential utility of what I am suggesting.

My sense is that we need to use the emerging and “hot” technical areas of genomics and protein-omics to determine what systems and biochemical substances are being turned on and turned-off during environmental exposures to toxicants. Combining the knowledge of these changes with information on the concurrent adverse and adaptive physiological effects in humans and animals models should start to reveal what this all means relative to the health and well-being of the exposed individual. I believe it will also clearly reveal the reality of hormesis. Indeed, it would make little sense to do any of these experiments without looking for (*i.e.*, hypothesizing) and quantifying a hormetic effect at low dose.

My sense is that all this it will also raise the level of complexity in risk assessment significantly. I believe it is going to take quite a bit of work to sort out the negative health effects that result from the induction or inhibition of multiple sites within humans and the animal models. Also, we already know that some negative health outcomes can be profoundly influenced by the characteristics of a person’s specific genome. Clearly, we are going to have to deal with the hyper- and hypo- susceptible individuals. Indeed, it may be entirely possible that any reasonable and politically and economically practical exposure limit will only protect “nearly all” persons because of this reality. At least we may have some idea as to who the hyper-susceptible individuals might be, assuming that individual genetic testing will almost certainly happen in the future. Given that knowledge we should be able to protect or at least inform and thus potentially safeguard everyone.

We would, of course, not test every chemical of interest unless the tests were exceedingly cheap. We should, however, test and fill out a matrix of chemical classes. Doing this, we will eventually have enough data and knowledge to start to interpolate or otherwise bridge within the emerging pattern of information, which I have no doubt will include hormesis.

So as a final comment, I believe that the use of hormesis as a default hypotheses is ultimately coming we simply have to first change the entire toxicological testing paradigm. I believe that change is also approaching.

Reference:

M.A. Jayjock, P.G. Lewis and J.R. Lynch: Quantitative Level of Protection Offered to Workers by ACGIH Threshold Limit Values (TLV®) Occupational Exposure Limits, *Am. Ind. Hyg. Assoc. J.* 62 : 4-11 (2001).