Hormesis—Basic, Generalizable, Central to Toxicology and a Method to Improve the Risk-assessment Process

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Hormesis, a dose–response phenomenon characterized by a low-dose stimulation and a high-dose inhibition, has been the object of controversy due to its challenging of basic understandings of the dose–response relationship and implications for risk assessment. The author addresses issues relating to the definition of hormesis, the relationship of hormesis to risk assessment and risk management, and the generalizability of hormesis within the toxicological literature. *Key words*: hormesis; U-shaped; j-shaped; biphasic; low doses; stimulatory; risk assessment.

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In a recent paper in *IJOEH*, Axelrod et al.[1] presented a perspective on hormesis which argued that:

> "beneficial" hormetic responses should not be incorporated into risk assessment because of complexities associated with the risk-assessment process such as dealing with developmental and interindividual variation, multiple chemical exposures, and multiple organ susceptibilities; and
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> hormetic responses should not be seen as adaptive in nature and universal in occurrence; if they were, then hormetic responses could by used as the default assumption in risk assessment; the authors present several examples that they believe support their interpretation.

The major general scientific points articulated in the paper, captured in the above two summary statements, give a misleading picture of current developments in the field and can lead to a flawed understanding of the concept of hormesis and its potential risk-assessment implications. The paper does not accurately describe our views on how hormesis should be defined and its relationship to risk assessment and risk management. In the paper entitled "Defining Hormesis"[2] we stated in the abstract that hormesis is an adaptive response characterized by a biphasic dose–response relationship having reasonably well defined quantitative features. Further, it was explicitly stated that the issue of beneficial/harmful responses should not be part of the definition of hormesis, but reserved to a subsequent evaluation of the biological and ecological context of the response. The first major section of that same paper has a relevant and critical subtitle, "Decoupling beneficial effects from the definition of hormesis." In fact, when the paper "Defining Hormesis" was published, there were six independent expert commentaries that addressed the proposed definition. While there was a general, but not complete, agreement with the definition, the statement of Chapman[3] is worth quoting:

> The definition of hormesis proposed by Calabrese and Baldwin[2] is, appropriately, purely scientific. Removing beneficial/harmful effects from the definition of hormesis is a major, key step forward, which will change the debate regarding hormesis significantly. Previously hormesis has been generally defined in terms of potential beneficial effects. Such definitions confused the phenomenon of hormesis with its possible outcomes.
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> However, there should now no longer be confusion between scientific issues (hormesis itself) and management issues (the significance of hormesis). It is now clear that the possible outcomes of hormesis, whether or not hormesis has beneficial (or harmful) effects to the individual, other individuals, or to populations and communities, comprise a separate issue. To put this in terms of risk assessment and risk management, determining whether or not hormesis occurs is a risk assessment issue; determining the significance of hormesis is a risk management issue (the 'more advanced stage of the analysis' noted by Calabrese and Baldwin[2]).

Consistent with these earlier citations, my recent paper on hormesis and the concept of a default risk-assessment model[4] indicates that once a determination is made that the dose response is hormetic the next issue "to resolve is whether the response below the NOAEL (i.e., hormetic stimulation) was considered beneficial, neutral effect or adverse." Nonetheless, Alexrod et al.[1] blur the definition of hormesis that decouples the scientific assessment of hormesis from

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risk-management decisions about benefit/harm; secondly, they ignore the entire range of public health consequences (i.e., beneficial, harmful, or neutral) that the hormetic model makes available.

The widespread recognition of hormetic dose responses by numerous and highly credible toxicologists does not disregard scientific or public health considerations. In fact, just the opposite is the case, as it provides risk assessors for the first time with the toxicological power to consider the entire dose–response continuum. Simply continuing to make inappropriate assumptions about what happens at low doses falls far short of what is needed and what we are capable of doing.

Prior to our work on hormesis, regulatory agencies, such as EPA, assumed "functional" universality for the threshold model in dealing with non-carcinogens and LNT modeling for carcinogens. We demonstrated not only a frequency of hormetic dose responses in the toxicological literature of about 40% using rigorous a priori entry and evaluative criteria,[5] but also that the hormetic model was far more common than the "universal" threshold model.[6] But contrary to that which is suggested in the title of the Axelrod et al.[1] paper, we have not indicated that hormesis is universal, nor could we. There are situations when the hormetic hypothesis can't be evaluated, such as when background rates in control groups are very low. Also, because hormetic stimulation is generally modest, there are numerous design constraints that make difficult, if not impossible, differentiation of normal variability from treatment effects. Because of such constraints, discussions of "universality" must be deferred in favor of consideration of generalizability. However, the data indicate that the hormetic dose–response model clearly out-competes its most serious competitors in head-to-head competition and is generalizable, being independent of biological model, endpoint measured, and chemical/physical stressor.

The hormetic model is not an enemy to the public health community. Quite the contrary, it brings more information, strength, and options to the fields of toxicology and risk assessment. If properly used, it would enhance public health. The protectionist public health philosophy that guides current risk-assessment practices does not follow the data; rather, it follows an unscientific belief that only lower is better. It has become clear that this is not "universally" true and may be generally wrong and potentially wasteful of resources to improve the overall well-being of society.

The hormetic model can effectively allow incorporation of any of the technical issues raised by Axelrod et al.[1] Hormetic responses of population subgroups considered at increased risk have been widely assessed and demonstrated.[7] A number of peer-reviewed studies have demonstrated hormetic dose responses for highly complex mixtures as well as discrete mixtures of a few specific agents. Likewise, hormetic effects have occurred in multiple organs, over different dose ranges as well as with multiple agents displaying similar or nearly identical mechanisms and different potencies. These specific toxicological permutations do not challenge the scientific basis of hormesis or its use in hazard assessment or other risk-assessment applications. They are simply part of the normal assessment process.

Where do we stand at present? The concept of hormesis continues to gain scientific strength, as evidenced in our recent assessment of the hormesis database with nearly 6000 examples[8] and major forthcoming reviews on hormesis and immune responses[9] and within tumor cell lines,[10] as well as a vast array of previously published studies on numerous toxic substances and pharmacologic agents, with detailed mechanisms reported for many.[11,12] The key in these evaluations is that hormesis is not seen by only one research group, but by many hundreds of leading researchers independently publishing in rigorous and highly prestigious journals, using different models, endpoints, and agents. It is a phenomenon that is extremely generalizable and built within the context of evolutionary biology and is therefore selected for and adaptive. Public health scientists need to focus first on the biology of hormesis and allow the data to stimulate thinking concerning potential implications. My principal concern is that the attitude of fear that embodies the paper of Axelrod et al.[1] has the potential to deny scientists their natural curiosity about this biological phenomenon and to see it only though political eyes. To do this will serve neither the scientific and biomedical communities nor the broader interests of society.

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