HORMESIS-DOES IT HAVE RELEVANCE AT THE POPULATION-, COMMUNITY- OR ECOSYSTEM-LEVELS OF ORGANIZATION?

John P. Giesy, Ph.D.
Department of Zoology,
National Food Safety and Toxicology Center and
Institute of Environmental Toxicology,
Michigan State University,
East Lansing, MI, 48824
Tel: 517-353-2000
Fax: 517-432-1984
Email: jgiesy@aol.com

In his paper entitled "The Impact of Hormesis to Ecotoxicology and Ecological Risk Assessment (ERA)", Peter Chapman has called for changes in the risk assessment paradigm to accommodate the concept of hormesis. As he points out in his paper, there are certain parallels between hormesis and some "low-dose effects" that have been described at the individual, population and ecosystem levels of organization. These low-dose effects and how to interpret them in risk assessment paradigms have become the fulcrum of a debate between those who think a shift in the standard toxicological paradigms of dose-response relationships and receptor-mediated responses is required and more traditional toxicologists who maintain that no such shift in paradigm is required. This is due, in part, to differences in opinion over whether increases in a response parameter near the No Observable Effect Concentration (NOEC) are adverse or not. One of the basic tenants, on which traditional toxicology is built is the concept of the dose-response relationship. Furthermore, there is the concept of a threshold, below which no adverse effects would be observed. Thus, this is where the concept of hormesis potentially comes into play.

The debate over safety of chemicals in the environment ranges from two extremes. There are those who believe that, by their very nature chemicals must cause adverse effects but that they may be subtle or are beyond the ability of modern science to measure. At the other end of the spectrum are those who believe that there are thresholds below which organisms can be exposed indefinitely to a stressor without adverse effect. More recently, the debate over the potential for adverse effects from low-dose exposures has been subsumed into the debate of environmental endocrine disruptors (Colborn et al, 1996). Specifically, it has been suggested, by some, that there is, in fact, no threshold for endocrine-modulating effects. Furthermore, there has been discussion, particularly about compounds that might be weak hormone receptor agonists and thus mimic hormones that there is a "less is more phenomenon" where exposure to lesser concentrations of a hormone mimic could result in a greater response than greater concentrations. Most of the compounds being discussed in the debate are weak estrogen receptor (ER) agonists, such as *o,p* DDE, bisphenol-A and 4-nonylphenol. It has been suggested that these compounds can cause an inverted "U"-type response. In fact, we have observed this phenomenon for fecundity of fathead minnows exposed to 4-nonylphenol (Giesy, et al. 1999). The primary issue are whether this phenomenon occurs through a receptor-mediated process and whether this phenomenon would affect the way risk assessments are currently conducted. The debate is, in my opinion, a misunderstanding. It seems that the misunderstanding stems from assuming that low-level effects are mediated by the same mechanism as those observed at greater concentrations. It is further assumed that compounds that have been identified as weak hormone receptor agonists only cause effects through this mechanism of action, when in fact, there may be multiple mechanisms of action involved For instance, the herbicide atrazine can cause estrogenic effects *in vitro* and *in vivo* (Villeneuve et al., 1998), but does not bind to the ER. In the case of atrazine, it has been found that it can activate CYP19 (aromatase), the enzyme responsible for transforming testosterone into estradiol (Sanderson et al., 2000). In the case of 4-nonylphenol, it is likely that the low-level effects observed in fish are due to a mechanism other than that mediated through the ER.

Hormesis has been observed in a wide range of responses in cells, tissues and individuals of a wide range of species (Calabrese & Baldwin 2000). The issue is whether the concept and terminology are appropriate to be applied to other levels of organization, such as populations, communities or ecosystems (Bartell, 2000). Hormetic responses have been described for ecosystems, however, as will be discussed below, these are not strictly analogous to the responses that have been described for individuals or colonial populations (Bartell, 2000; Stebbing, 1997; Stebbing, 2000). The question to be addressed here is whether extension of the concept and terminology of hormesis applied to individual organisms can or should be extended to ecosystems. As is pointed out by Bartell (2000), interpretations of hormesis within an ecosystem context cannot be made independent of the context of ecosystem.

While the concept of non-monotonic effect functions could be accommodated into a revised paradigm of ecological risk assessment, the question is whether the term hormesis would be the most appropriate term fo

these types of responses. While I do not know the exact etymology of the word, hormesis has generally been applied to individual organisms or populations. To expand the term to responses of ecosystems is problematic, at least as it applies to risk assessment, because it requires a frame of reference. The fact that one species increases in number may be at the expense of another species. Thus, requiring a value judgment on what is considered positive and what is considered negative. Without knowing the consequences of the change, I would think most risk assessors would consider any change from the normal range of variation, especially those associated with human activities to be adverse or undesirable. An alternative terminology has been suggested. The concept of non-monotonic responses of ecosystems to forcing functions is embodied in the "subsidy-stress" hypothesis developed by Odum (Giesy and Odum 1980). This concept was developed to describe responses of ecosystems exposed to all types of stressors, chemical and otherwise.

From an ecological risk assessment point of view, I think that incorporating the concept of increases and decreases in a measurement endpoint need to be considered. I agree with Chapman that assessing the magnitude of response on a monotonically increasing scale as a function of exposure is not relevant. Thus, it is easy to conceive of a paradigm shift to include these types of non-linearities. What will be more difficult is determining the ecological relevance of such changes. Since determining the relevance, importance or desirability or permissibility of negative changes is sufficiently difficult, the challenge will be to determine the significance of hormetic changes in a social and economic context. I would submit that we simply do not understand the interconnections or magnitudes, directions or rates of change that would be expected in linked state variable to make intelligent decisions in the near-term, let alone in the longer-term. Thus, from an ecological risk assessment perspective, the concept of hormesis will not be particularly useful. In these situations, any change in one state variable or forcing function would be expected to result in changes of state for the entire system. Without knowledge of what these changes might be, and without defining the value system on which they will be evaluated, all changes must be considered likely to result in changes, the desirability of which can not be predicted.

When discussing hormesis in response to "stressors" within an ecological risk assessment paradigm, the stressor would need to force the ecosystem beyond the normal functioning range. That is, if the stressor were temperature and the ecosystem had evolved to function within a defined range of varying temperatures, then temperature might not be classified as a stressor unless it forced the structure and or function of the ecosystem to a state that was sufficiently different from the original state that it would not return to the original, unperturbed state, within a prescribed period of time. The major difference between hormesis at the individual level of organization and that of the ecosystem is the differences in defining fitness. Scientists have derived definitions of fitness for individuals that do not apply to ecosystems. This does not mean that an overall fitness could not be defined for ecosystems such that exposure to forcing functions could not cause increases as well as decreases in fitness. For instance, the fitness of ecosystems could be defined as changes in resistence or resilience of ecosystem structure or function (Maguire et al, 1980, Bowling et al, 1980).

One of the major issues, as pointed out by Chapman (2001) of extending the concept of hormesis to populations, communities and ecosystems is determining if the hormetic response is an adverse, positive or neutral response. I would argue, that this is not only a scientific issue, but one of values and perception and point of view. That is, what may be an advantage for one species may result in adverse effects on other species. Furthermore, short-term responses deemed to be positive or desirable by one species, such as humans may result in long-term changes in the stability or state of an ecosystem, that might ultimately result in changes that are deemed negative.

While hormesis is often seen when one measures a single parameter for a population exposed to a chemical toxicant, this can often be explained by over-compensation or even protection from another stressor. An example I have seen in my own work is the better survival of crayfish exposed to sub-lethal concentrations of zinc, which killed the fungus that grows on their gills under laboratory conditions (Giesy et al 1980). Again in an ecosystem context, I do not know if this would be considered a hormetic response since one component of the ecosystem, the fungus, has disappeared from the system. Another example of such an ecosystem-level response is eutrophication. In it's earliest stages, slight enhancement in primary production result in enhanced secondary production of economically desirable (harvestable) species. Subsequent shifts in communities can ultimately result in a complete shift of the ecosystem to another state (dystrophy) which can eliminate the desirable species altogether. Currently, fisheries managers are debating whether curtailment of phosphorus entering the North American Great Lakes has been too great because it is limiting the overall productivity of the system and resulting in less harvestable biomass than could be sustained if the phosphorus loading were greater. The problem with assessing the desirability of these various possible states is that it is based on a short-term view and the egocentric position of certain groups of humans.

While I agree with much of what Chapman has written about extending the paradigms for ecotoxicology and risk assessment, I think that neither the term nor the concept of hormesis is useful beyond the individual (including colonial organisms). Populations, communities and ecosystems have properties that individuals do not have and individuals exhibit responses to stress that are not possible in populations, communities or ecosys-

tems. Specifically, individuals do not exhibit mortality, which is a rate. Individuals either survive or they do not. Furthermore, individuals are an integrated system with physiological and signal-transduction systems that integrate and coordinate the adaptive responses of individuals to their environments. Ecosystems have no such systems. Individuals have evolved to adapt to ever-changing environments to survive. Ecosystems represent the abiotic and biotic result of such adaptations.

While there is no formal definition of hormesis that I have been able to find in dictionaries of the English language, a working definition is the increase in a metric due to exposure to a stressor, chemical or otherwise. This is often represented as an adaptive response, that "overshoots" what may be necessary to respond to the stressor. The concept is consistent with the general adaptation syndrome proposed by Hans Selye (1976). Survival is a concept that is unique to individual organisms, and it is within this context that stress serves as a selective agent. Ecosystems do not have adaptoive responses to stressors and they are not selected for, at least not in the same way organisms are. In fact, it could be argued that ecosystems are the aggregate state of adaptation and selection at the individual level of organization. Therefore, I think that the concept of hormesis is not directly applicable to ecosystems and the term hormesis should be reserved for adaptive responses of individual organisms. There is enough confusion over concepts and terms without ascribing different meanings to terms that are already in use. Instead, what I think should be done, is to take the very valid suggestions of revising how ecotoxicology is practiced that are given by Chapman. Specifically, it would be appropriate to evaluate the subsidy-stress concept, relative to responses of ecosystems to stressors. Furthermore, it is important to address the issue of low-dose responses of individuals to stressors. This may mean a reevaluation of the methods for deriving NOECs and Lowest Observable Effect Concentrations (LOECs) and how risk assessments are conducted. Specifically, I agree with Chapman, that it is important to be sure that the entire dynamic range of effects is investigated. That means conducting studies with more doses near to the actual NOEL. Certainly, I would agree that these low-dose effects need to be investigated and evaluated. However, the question is whether to refer to them as hormesis. Because, survival of species is, in part, a function of survival of populations under stress, referring to adaptive responses that are manifested at the individual-level, but measured in studies as the aggregate response of a population, I think using the term hormesis to describe such phenomena is appropriate.

As a point of departure, I would suggest that any response that moves an organism out of it's normal homeostatic range or requires expenditure of energy or mobilization of stored resources be viewed as a negative response. As an example, I will draw upon results of my own research. When fathead minnows were exposed to 4-nonylphenol, an "inverted U" dose-response relationship was observed for egg production (Giesy et al 1999). A the lesser doses egg production was increased, while a greater concentrations, egg production was completel y eliminated. This could be considered a hormetic response. The issue, relative to ecotoxicology and risk assessment is where to set the NOEC or "allowable" concentration. As is pointed out by Chapman the standard paradigm applied in ecotoxicology and ecol gical risk assessments of assuming a monotonic, increas in response as a function of exposure, is clearly violated. The effect caused by 4-nonyl phenol seems to be one of increasing circulating concentrations of 17b-estradiol (E2), which, at moderately increased concentrations facilitates recrudescence (Kramer et al 1998). Estradiol is not a gonadotropin, but rather, at greater concentrations resets the recrudescence cycle, such that there is a greater preponderance of primary oocytes. Depending on the magnitude of change or timing of the change, these types of responses might be negative, positive or neutral, relative to the fitness and survival of individual genotypes or the species under particular local environmental conditions. Thus, while the standard types of statistical analyses may not be appropriate to data of this type, from an ecological risk assessment perspective, a y alteration in the timing or number of eggs may have negative repercussions. For instance, an acceleration of the recrudescence cycle in females might put them out of phase with males, such that while there are more eggs produced, they may not be fertilized. In addition, accelerating the number of eggs produced, might result in smaller, less "fit" eggs. Thus, for purposes of ecological risk assessments even an increase in this parameter, a decrease of which is normally considered to be negative, might result in adverse outcomes. Finally, to determine, in a risk assessment framework, what is adverse requires a framework of values and perspective. Our egocentric predicament does not allow humans to make these judgements with any degree of predictability relative to ecosystem-level responses.

In conclusion, neither the concept, nor the terminology of hormesis should be applied to ecosystem-level responses to stressors. Furthermore, while ecological risk assessment procedures need to be improved and likely will continue to improve as more information about the functioning of ecosystems and their responses to stressors is learned, the results of these assessments will be more predictive and protective. However, a paradigm shift to accommodate hormesis in these assessments is not needed. In fact, hormesis is not the major cause of uncertainties in either ecotoxicology or ecological risk assessments.

REFERENCES

Bartell SM. 2000. Are Ecosystems Hormetic? *Human and Ecological Risk Assessment* 6:237-43.

Bowling JW, Giesy JP, Kania HJ, Knight RL. 1980. Large Scale Microcosms for Assessing Fates and Effects

of Trace Contaminants. In: Giesy JP (ed), Microcosms in Ecological Research, pp 224-247, 52, CONF-781101, Department of Energy Technical Information Center, Oak Ridge, TN.

Calabrese EJ, Baldwin LA. 2000. History of chemical hormesis. *Hum. Experiment. Toxicol.* 19:2-31.

Colborn T, Dumanoski D, Myers JP. 1996. Our Stolen Future. Dutton Book, New York, NY, pp. 306.

Giesy JP, Bowling JW, Kania HJ. 1980. Cadmium and zinc accumulation and elimination by freshwater crayfish. *Arch. Environ. Contam. Toxicol.* 9:683-97.

Giesy JP, Odum EP. 1980. Microcosmology: The Theoretical Basis. In: Giesy JP(ed), Microcosms in Ecological Research, pp1-13. 52, CONF-781101, Department of Energy Technical Information Center, Oak Ridge, TN.

Giesy JP, Pierens SL, Miles-Richardson S, *et al.* 1999. Effects of 4-nonyl phenol on fecundity and biomarkers of estrogenicity in fathead minnows (*Pimephales promelas*). *Environ. Toxicol Chem.* 19:1368-77.

Kramer VJ, Miles-Richardson S, Pierens SL, Giesy JP. 1998. Reproductive impairment and induction of alkaline-liable phosphate, a biomarker of estrogen exposure, in fathead minnows (*Pimephales promelas*) exposed to waterborne 17b-estradiol. *Aquatic Toxicol.* 40:335-60.

Maguire B, Slobodkin LB, Morowitz HJ, More B, Botkin DB. 1980. A New Paradigm for the Examination of Closed Eco-Systems. In: Giesy JP (ed), Microcosms in Ecological Research. pp. 30-68. Department of Energy Symposium Series, 52, Conf-781101, Department of Energy Technical Information Center, Oak Ridge, TN.

Nichols KE, Snyder EM, Miles-Richardson S, et al. 1999. Effects of Municipal Wastewater Exposure in situ on the Reproductive Physiology of the Fathead Minnow (*Pimephales promelas*). Environ. Toxicol. Chem. 18:2001-12.

Sanderson. JT, W Seinen, JP Giesy and M. van den Berg. 2000. 2-chloro-S-Triazine Herbicides Induce Aromatase (*CYP-19*) Activity in H295R Human Adrenocortical Carcinoma Cells: A Novel Mechanism for Estrogenicity. *Toxicolo. Sci.*54:121-27.

Selye H. 1976. Stress in Health and Disease. Butterworths. Boston and London.

Stebbing ARD. 1997. A theroy for growth hormesis. *Belle Newslet.* 6:1-11.

Villeneuve, DL, Blankenship AL and Giesy JP. 1998. Estrogen receptors-environmental xenobiotics. pp. 69-99, Chapter 4 In: M.S. Denison and W.G. Helferich (eds.). Toxicant-Receptor Interactions and Modulation of Gene Expression. Lippincott-Raven Publishers, Philadelphia.

HORMESIS IN ECOLOGICAL RISK ASSESSMENT: A USEFUL CONCEPT, A CONFUSING TERM, AND/OR A DISTRACTION?

Charles A. Menzie, Ph.D.
Menzie-Cura & Associates
1 Courthouse Lane
Chelmsford, MA 01824
Tel: 978-322-2856
Fax: 978-970-2791
Email: charliemen@aol.com

This paper is written in response to Chapman (2001) who provides useful insights into the application of hormesis concepts to ecotoxicology and ecological risk assessment. I found myself agreeing with some points, disagreeing with others, and wondering whether the term or the concept of hormesis was useful for scientific inquiry and environmental policy.

The term – which refers to stimulatory responses at low doses and inhibitory or otherwise negative effects at high doses has had an interesting history (Calabrese and Baldwin, 1999). In formulating my comments I considered the reasons why hormesis is of interest and I surmise it is largely because of the substantial uncertainty associated with low-dose exposures. This uncertainty stems, in part, from extrapolations currently made in human health risk assessments wherein data are available at high or intermediate doses but the effects of interest are those associated with much lower doses. Scientific policy decisions have typically involved the application of models to extrapolate from the data range to these low doses. In the case of cancer risk, these models have typically assumed no-threshold effects and linear extrapolations. Much debate has centered on such extrapolations. The uncertainties associated with application of these models are among the reasons why Deisler (2000) encouraged the exploration of hormesis.

Assuming that policy and technical issues surrounding low-dose extrapolations in human health risk assessment are the genesis of recent discussion concerning hormesis, how do such discussions bear on ecotoxicology and ecological risk assessment? I explore this by first