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Conceptual Clarification and Policy-Related Science: The Case of Chemical Hormesis

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This paper examines the epistemological warrant for a toxicological phenomenon known as chemical hormesis. First, it argues that conceptual confusion contributes significantly to current disagreements about the status of chemical hormesis as a biological hypothesis. Second, it analyzes seven distinct concepts of chemical hormesis, arguing that none are completely satisfactory. Finally, it suggests three ramifications of this analysis for ongoing debates about the epistemological status of chemical hormesis. This serves as a case study supporting the value of philosophical methodologies such as conceptual clarification for addressing contemporary scientific disputes, including policy-related scientific disputes that may be heavily influenced by social and political factors.

Introduction

In recent years, several factors have stimulated research concerning the biological effects of low levels of anthropogenic chemicals in the environment. First of all, recent research has associated very low doses of some chemicals, especially chemicals that "mimic" hormones such as estrogen, with phenomena such as reproductive cancer, low sperm counts in male organisms, alteration of immune function, and decline in species populations (see Birnbaum 1994; Colborn et al. 1996). Second, chemical manufacturers are being held accountable for the effects of toxic chemicals, so they need to determine the limits of their liability or responsibility. Third, new techniques are making it possible to measure the low-level effects of chemicals that could not be measured in the past. Fourth, risk management by government agencies such as the Environ-

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mental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA) has helped to reduce pollutant levels in the environment, so it is now more realistic for toxicologists to study the effects of these substances at lower doses.

This interest in the low-level effects of toxic chemicals has stimulated study of chemical hormesis (e.g., Stebbing 1982; Davis and Svendsgaard 1990; Calabrese and Baldwin 1998*b*). Although no current definition of 'chemical hormesis' is entirely satisfactory, the phenomenon is characterized by a chemical's production of low-dose biological effects that are the opposite of the toxic effects produced at higher dose levels by the same chemical (see figure 1).[1] Some researchers are suggesting that chemical hormesis is a generalizable phenomenon with significant policy implications (Calabrese and Baldwin 1999*b;* Stebbing 1997; Sielken and Stevenson 1998; Teeguarden et al. 1998), but other scientists have been slow to accept the legitimacy of such claims (Davis and Svendsgaard 1990; Davis and Farland 1998). The first section of this paper argues that much of this disagreement about the warrant for the existence and generalizability of chemical hormesis can be traced to conceptual confusion. In the hope of alleviating this confusion, the next section outlines seven distinct (though not mutually exclusive) concepts of chemical hormesis present in recent articles and argues that none of them are completely satisfactory. Finally, the last section argues that the conceptual clarification provided in this paper suggests at least three ramifications for ongoing debates concerning the epistemological status of chemical hormesis.

Clarifying these concepts and debates is important not only for its contribution to scientific understanding in disciplines such as epidemiology, toxicology, and pharmacology, but also because of the implications of this case study for public policy and for philosophy of science. The removal of the last one or two percent of any pollutant from the environment can be extremely costly. Therefore, an ongoing conflict exists between the medical and environmental communities on the one hand and the industrial community on the other hand regarding the importance of removing low levels of toxins from the environment. The hypothesis of chemical hormesis is central to this conflict, because the existence and general-

1. Alcohol provides a good example of this sort of dose-response. At low to moderate dose levels, alcohol appears to *decrease* human mortality rates *below* control levels. At higher doses, however, alcohol *increases* human mortality rates *above* controls (e.g., Gordon and Doyle 1987). Not all researchers would consider this to be a case of chemical hormesis, but it serves as a commonly-recognized example of the sort of dose-response curves that are characteristic of chemical hormesis (see figure 1).

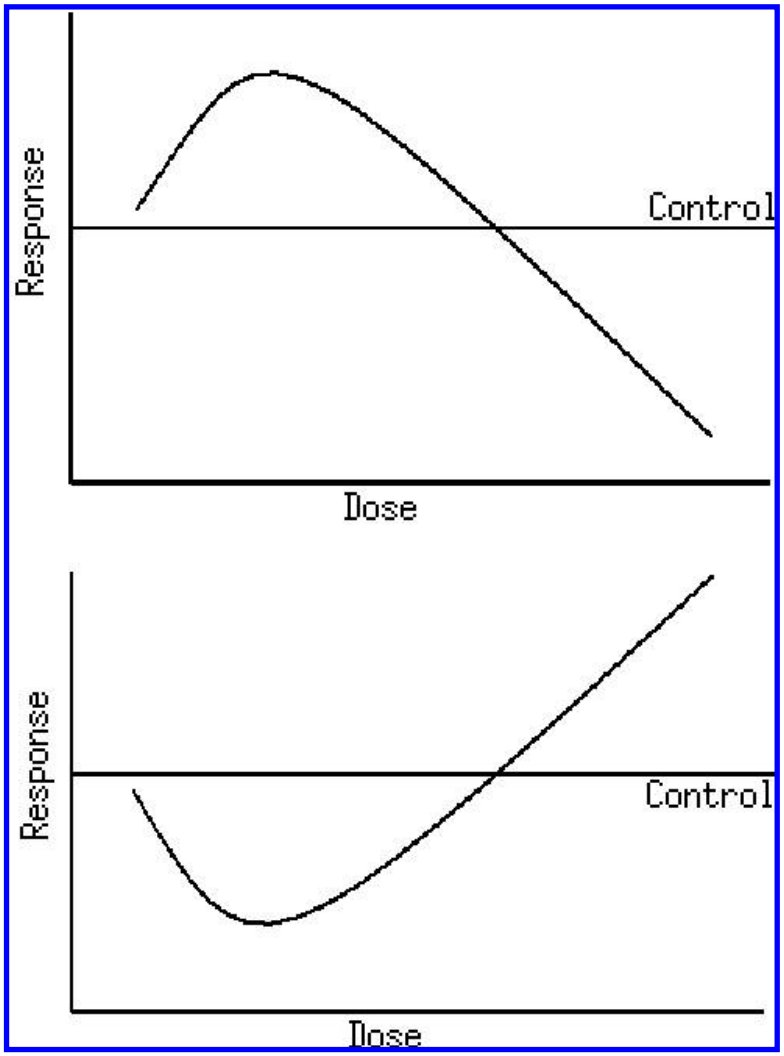

Figure 1. Examples of the general form of hormetic dose-response relationships. The bottom curve could represent the relationship between alcohol and human mortality, whereas the top curve could represent the hormetic effects of growth inhibitors on plant growth.

izability of chemical hormesis would support the claim made by the industrial community that low levels of contamination are not harmful (and are perhaps even *helpful!*). Furthermore, this examination contributes to the philosophy of science by illustrating the way that conceptual or epistemological analysis can reveal philosophical conflicts at the heart of scientific debates that appear to revolve around substantive facts. Ernst Mayr claims that much of the recent progress in evolutionary biology has been a result of *conceptual clarification,* not a consequence of improved empirical tests (1988). This paper provides a case study supporting the value of conceptual clarification in the evaluation of disputes even in a highly empirical and applied scientific discipline such as toxicology.

Finally, the conceptual clarification provided in this paper supports the efficacy of philosophical methodologies for addressing disputes over policy-related science. In her article on radiation hormesis (this issue, section 2), Kristin Shrader-Frechette draws attention to Deborah Mayo's (1991) division of thinkers who acknowledge the value-laden character of risk assessment into two groups. On one side, the "sociologists" insist that social and political values are inseparable from scientific hypotheses related to risk assessment (e.g., Wildavsky and Douglas 1984). On the other side, "metascientists" believe that methodological (as opposed to social and political) value judgments are sufficient for evaluating scientific hypotheses (e.g., Mayo 1991). Shrader-Frechette provides support for the metascientists' position by arguing that traditional philosophy-of-science analysis is sufficient for resolving the current dispute over radiobiological hormesis.

Similarly, this paper supports the efficacy of philosophical approaches (in this case, conceptual analysis) for addressing disputes in policy-related science. The first sections of the paper introduce some of the social and political factors that contribute to disputes over hormesis, but section III argues that, at present, conceptual clarification is sufficient for showing the evidence for chemical hormesis to be unconvincing. Use of the term 'chemical hormesis' in recent literature suggests the existence of one particular, relatively universal low-dose phenomenon, but careful attention to the multiple concepts of hormesis in use reveals that the existence of such a phenomenon is not supported by current research. Because the two primary sources of alleged hormetic biological effects are toxic chemicals and radiation, this paper and the accompanying article by Shrader-Frechette provide significant support for the claim that the philosophy of science, as opposed to sociology, is presently adequate for resolving scientific disputes related to hormesis.

One might object to the choice of philosophical methodology (i.e., conceptual clarification and analysis) employed in this paper by arguing

that it incorrectly presupposes that science is progressive only when scientific research proceeds with conceptual precision. However, this paper claims only that, at the present time, adequate evaluation of the chemical hormesis hypothesis and of its implications for public policy requires increased conceptual precision. This does not mean that conceptual "looseness" has not been beneficial for previous research concerning the hormesis phenomenon or that it cannot sometimes play a valuable role in scientific research in general.

I. The Role of Conceptual Confusion in Current Debates

This section summarizes recent debates about the hypothesis that chemical hormesis exists and is generalizable and argues that conceptual confusion plays an important role in these debates. To date, perhaps the most significant work on chemical hormesis has been done by Edward Calabrese and Linda Baldwin, who recently completed an extensive literature search designed to uncover evidence for chemical hormesis in previous toxicology research. They concluded that chemical hormesis "appeared to be highly generalizable" (1998*b,* p. 3) and that claims about "the concept of hormesis (i.e., low-dose stimulation/high-dose inhibition)" are at odds with the presuppositions underlying "the cancer risk assessment practices by United States regulatory agencies such as the EPA, FDA, and OSHA which assume that cancer risk is linear in the low-dose area" (1998*b,* p. VIII-1). Similarly, Justin Teeguarden, et al. recently claimed that the evidence for hormesis in recent literature "challenges current approaches to carcinogen testing that are limited in their usefulness by their narrow focus on *linear* dose responses and toxic effects. Indications of hormesis in carcinogenesis further legitimize the notion that current *linear* low-dose approaches to risk assessment and human drug safety studies are flawed" (1998, p. 257, italics added). Similar claims can be found in many other articles (e.g., Sielken and Stevenson 1998; Johnson and Bruunsgaard 1998; Appleby 1998).

So far, however, governmental agencies have been slow to accept the evidence for chemical hormesis. Ortwin Renn reports that "regulatory agencies prefer to ignore this phenomenon as not yet proven or to deem it irrelevant for pursuing their public mandate" (1998, p. 431). J. Michael Davis and William Farland, two EPA scientists, do not think that present information is sufficient to justify the hypothesis that chemical hormesis (which they refer to as BELLE—Biological Effects of Low-Level Exposures) is a replicable phenomenon: "At present it is not clear that general principles pertaining to BELLE exist for United States EPA scientists to consider. Thus, those who wish to advance the consideration of BELLE in public health regulatory contexts bear a certain burden of proof to show

enough evidence to support a conclusion that a benefit actually results from low-level exposure to an environmental pollutant" (Davis and Farland 1998, p. 380). In short, the warrant for chemical hormesis is a matter of dispute.

In a series of recent papers (2000*a*; 2000*b*; 2000*c*; 2000*d*; 2000*e*) designed to justify their recent research in support of hormesis, Calabrese and Baldwin canvass the history of the biological hypotheses of both chemical and radiation hormesis from the late nineteenth century to the present. They suggest several explanations for the temporary demise of each hypothesis during the middle decades of the twentieth century. Calabrese and Baldwin claim that the demise of the radiation hormesis hypothesis is largely understandable, given its limited database and the difficulty of reproducing findings associated with the hypothesis (2000*e,* p. 92). Shrader-Frechette (this issue, section 5) elucidates a number of other reasons that this demise continues to be understandable, including the fact that radiation hormesis conflicts with a number of studies that show harmful results of very low doses of ionizing radiation.

In contrast, Calabrese and Baldwin claim that the chemical hormesis hypothesis has been linked to so much scientific evidence and has been associated with the laboratories and students of such influential scientists (including Louis Pasteur, Robert Koch, Wilhelm Ostwald, and Charles Richet) that its demise is initially quite surprising (2000*e,* p. 92). In order to account for this demise, Calabrese and Baldwin rely heavily on sociological explanations (see e.g., Calabrese and Baldwin 1999*b,* p. 727). First, some hormesis researchers and many proponents of the medical practice of homeopathy attempted to use hormesis to explain the effects of homeopathic remedies, thus linking hormesis with a disreputable and severely-criticized medical research program (2000*e,* p. 92). Second, the low-dose region of dose-response curves did not, in the middle of the twentieth century, appear to have many practical implications that could provide an incentive for further research (2000*b,* p. 37). Third, close educational connections between important critics of chemical hormesis (e.g., A. J. Clark) and many of the biostatisticians who pioneered the development of dose-response models further minimized the potential for hormetic effects to be integrated into mainstream toxicological research (Calabrese and Baldwin 2000*b,* p. 37).

On one hand, this paper does not deny the contributions that Calabrese and Baldwin's sociological explanations may provide for explaining many features of hormesis debates. On the other hand, it does argue that, at present, philosophy-of-science analysis is sufficient for rejecting the chemical hormesis hypothesis, because conceptual analysis pinpoints the insufficiency of current evidence for any particular hormetic phenomenon.

First, examination of the concepts used by proponents and opponents of the hormesis hypothesis suggests that they tend to use different concepts of chemical hormesis. Proponents of chemical hormesis often focus on *mechanistic* concepts of chemical hormesis that associate it with one or two relatively unitary sets of phenomena. For example, Calabrese and Baldwin tried to group the instances of chemical hormesis that they found in their literature search into two "broad types"—"overcompensation hormesis" and "direct stimulation hormesis" (1998*b,* p. 1; see also Calabrese and Baldwin 1998*c*; Stebbing 1997). In contrast, opponents of chemical hormesis tend to employ *operational* concepts that emphasize a multiplicity of phenomena that might be considered hormetic. EPA scientists prefer to speak of "U-shaped dose response curves"[2] in general, or they use the generic term "biological effects of low-level exposures" (Davis and Svendsgaard 1990; Davis and Farland 1998).

Although it is very difficult to speculate about the reasons for these conceptual differences, it appears that they are probably not the result of deep methodological disagreements between, for example, proponents of a mechanistic approach to biological science as opposed to proponents of a more epidemiological, "empiricist" approach. As section II of this paper indicates, both Calabrese and Baldwin and Davis and Svendsgaard employ both operational and mechanistic concepts throughout their work. Therefore, it appears that these researchers may *focus* on different concepts in some of their *arguments* because of the differing implications that these concepts suggest for the legitimacy of the hormesis hypothesis.

These conceptual differences between proponents and opponents of chemical hormesis contribute to epistemological disputes in at least two ways. First, the use of different concepts tends to support different conclusions about the *plausibility* that chemical hormesis exists as a replicable phenomenon, given current evidence. Calabrese and Baldwin's *mechanistic* concept of "overcompensation" hormesis is based on Anthony Stebbing's suggestion that it is adaptively advantageous for organisms to develop

2. These curves are called "U-shaped dose-response curves" because the biological effects of toxic chemicals *equal* the level of controls at some dosage close to zero, the effects drop *below* the level of controls at slightly higher doses, and the effects rise to levels *above* the controls at still higher doses, thus producing a U-shaped curve. The effects of alcohol on human mortality could be represented by a U-shaped curve of this sort (see the bottom curve in figure 1). Furthermore, a "U-shaped dose-response curve" could also be inverted, thus representing very low dose effects that rise *above* the levels of controls and high dose effects that drop below the levels of controls (see the top curve in figure 1). For example, if a toxic chemical inhibited the growth of an organism at high doses but increased its growth at extremely low doses, it would produce a dose-response curve with an inverted-U shape. Throughout this paper, I will follow the example of Davis and Svendsgaard (1990) and refer to both upright- and inverted-U curves as U-shaped-dose-response curves.

regulatory processes that temporarily "overreact" to stressors, thus producing stimulation at low doses (Stebbing 1997). Given the plausibility of this evolutionary mechanism for chemical hormesis, it tends to support a conclusion in favor of the existence of chemical hormesis (Calabrese and Baldwin 1998*c,* p. 355). In contrast, Davis and Svendsgaard examine the legitimacy of the hormetic hypothesis solely by looking for evidence of U-shaped dose-response curves. Given this concept of chemical hormesis, they suggest that chemical hormesis may not be a replicable phenomenon, even though evidence exists for hormetic-looking phenomena, because many cases of U-shaped dose-response curves may be spurious or may result from confounding factors and complex interactive effects of chemicals (1990, p. 75–77).

Second, the different concepts employed by proponents and opponents of chemical hormesis suggest different conclusions about the *generalizability* of chemical hormesis given current evidence. On the one hand, Calabrese and Baldwin's isolation of two "types" of hormetic phenomena implicitly suggests that chemical hormesis can be associated with two relatively unitary sets of phenomena. This in turn suggests that hormesis might occur consistently under the conditions that produce those two phenomena (overcompensation and direct stimulation). Having found evidence for hormetic effects of each type in previous toxicology studies, Calabrese and Baldwin concluded that hormesis appeared to be highly generalizable (1998*b,* p. 3). On the other hand, the frequency of chemical hormesis is much more difficult to justify if one employs the operational concepts favored by opponents of chemical hormesis. For example, Davis and Svendsgaard report numerous different mechanisms (as well as invalid study designs) that might explain the U-shaped dose-response curves sometimes observed in toxicology studies. By emphasizing the multiplicity of factors that might produce occasional U-shaped dose-response curves, they cast doubt on the likelihood that chemical hormesis is a unitary explanatory phenomenon for which a specifiable frequency of occurrence can be given (1990, p. 75–77).

II. Conceptual Clarification of Chemical Hormesis

If conceptual confusion is hindering epistemological debates about the existence of chemical hormesis, then it is important to understand the precise nature of this confusion in order to determine its implications for the truth or falsity of claims about hormesis. This section attempts to distinguish seven distinct (though not mutually exclusive) concepts of chemical hormesis found in recent articles. I will call these concepts (1) "U-shaped-dose-response-curve hormesis," (2) "low-dose stimulation/high-dose inhibition hormesis," (3) "beneficial hormesis," (4) "over-

compensation hormesis," (5) "direct-stimulation hormesis," (6) "multiple-effects hormesis," and (7) "adaptive hormesis." For the sake of analysis, this paper groups the first three concepts as operational, the second three as mechanistic, and the last concept as genetic (i.e., focusing on origination); however, the notion of an "operational" concept as opposed to a "mechanistic" concept is not developed here in any special, technical sense. For the purposes of this paper, an operational concept can be regarded as one that is defined in terms of its criteria of application, which in the case of hormesis involves the measurement of some biological endpoint; a mechanistic concept involves the isolation of a system in which hormetic phenomena are produced by the interaction of parts according to causal laws (see, e.g., Bridgman 1927; Wimsatt 1976; Bechtel and Richardson 1993). Elucidating these seven concepts, I argue that none of them are completely satisfactory, considering the present state of research concerning chemical hormesis. Section III suggests, however, that further specification and examination of *mechanistic* concepts may prove to be the most fruitful source of *future* research in support of the hormesis hypothesis.

The first and perhaps dominant concept of chemical hormesis, "U-shaped-dose-response-curve hormesis," is defined as any non-spurious biological effect of a chemical that produces opposite effects at higher doses (an effect of this sort can be represented by a U-shaped dose-response curve, where the x-axis represents dose and the y-axis represents effect on a biological endpoint). For example, lead exposure normally *increases* the latency of auditory and visual evoked potentials in the human brainstem, but children exposed to *very low* doses of lead exhibit *decreased* latency of auditory and visual evoked potentials (Davis and Svendsgaard 1990, p. 74). From the beginning, the study of "chemical hormesis" has revolved around the search for *U-shaped dose-response curves* of toxic chemicals (see Calabrese and Baldwin 1999*a*). This concept can still be found, both implicitly and explicitly, throughout the literature on hormesis. The criteria by which Calabrese and Baldwin examined studies for evidence of chemical hormesis were designed to accord hormetic status to *any* U-shaped dose response (1998*b,* p. III-4). In at least one article, they refer to hormetic responses as "U- or inverted U-shaped dose-response relationships" (Calabrese and Baldwin 1998*c,* p. 353). Davis and Svendsgaard addressed the issue of chemical hormesis by examining "U-shaped dose-response curves" (1990). Similarly, Johnson and Bruunsgaard associate hormesis with a low dose response "opposite to that seen at high doses" (1998, p. 263).

"Low-dose-stimulation/high-dose-inhibition hormesis" is a second concept of chemical hormesis, which I define as any instance of

"U-shaped-dose-response-curve hormesis" that involves the *stimulation* of an endpoint at *low* doses and *inhibition* of the same endpoint at *higher* doses. For example, at doses of 10^{-8}- 10^{-7} M, the cytotoxic agent Adriamycin inhibits cell growth, but it stimulates cell growth at doses of 10^{-10}–10^{-9} M (Vichi and Tritton 1989, p. 2679). This concept of chemical hormesis is very similar to the previous concept, but it excludes U-shaped dose- response curves that involve *low* dose *inhibition* and *high* dose *stimulation* (e.g., the bottom curve in figure 1). This might not seem to be an important stipulation, but this second concept has been one of the most influential in the literature on chemical hormesis. The term "hormesis" was originally proposed by Southam and Ehrlich in 1943 to refer to "the *stimulation* of biological processes by subinhibitory levels of toxicants" (Calabrese and Baldwin 1998*b,* p. 1, italics added; Southam and Ehrlich 1943). In a number of articles, Calabrese and Baldwin follow this definition and refer to chemical hormesis as "low dose stimulation/high dose inhibition" (1998*a,* p. 230; see also Calabrese, et al. 1987). Many other authors also use this second concept (e.g., Stebbing 1982; Foran 1998).

A third operational concept, "beneficial hormesis," can be defined as a *beneficial* low-dose effect caused by a chemical that produces harmful effects at higher doses. For example, some studies report that low to moderate intake of alcohol has beneficial effects (such as decreased mortality), whereas high alcohol intake has negative effects (Davis and Svendsgaard 1990, pp. 76–77). A number of authors use this concept of chemical hormesis (e.g., Teeguarden, et al. 1998; Turturro, et al. 1998), perhaps because of its relatively clear implications for public policy (see, e.g., Calabrese 1996). If beneficial low-dose effects could be shown to be generalizable, changes might be warranted in dose-response models, dose scales, and risk characterizations in risk assessment, along with changes in hazardous waste cleanup requirements and "changes in health criteria for all environmental standards" (Calabrese and Baldwin 1999*b,* p. 723; see also Sielken and Stevenson 1998, pp. 259–262).

Others warn, however, that the concept of beneficial hormesis may not be acceptable (Elliott 2000, pp. 191–192; Davis and Farland 1998, p. 380; Davis and Svendsgaard 1990, pp. 79–80). One obvious difficulty is that the concept of beneficiality appears to be *normative* as opposed to being straightforwardly *descriptive* or *empirical;* therefore, it may be difficult to provide uncontroversial criteria for what is and what is not a beneficial response. Even if this initial difficulty is overcome, however, three further problems remain. First, it is very difficult to determine whether or not a particular response is actually beneficial; a response might appear to be beneficial in the *short* term but prove to be harmful in

the *long* term. Second, an apparently beneficial response could involve *side effects* that are ultimately deleterious. For example, Calabrese and Baldwin note that "stimulation of detoxifying enzyme levels observed in the larval form of a species would be evaluated for its hormetic potential even though this increased metabolic activity, while beneficial in the short-term, may have a detrimental effect on other endpoints" (1998*b,* p. II-5). Third, because of the *varying circumstances and physiological characteristics* of different individuals, the evaluation of a particular effect as "beneficial" or "harmful" could vary from individual to individual. For example, alcohol intake tends to decrease blood pressure, so moderate intake of alcohol might significantly decrease the mortality rate of those who suffer from hypertension but moderately increase the mortality rate of some other population groups. Or, as Davis and Svendsgaard point out, daily intake of aspirin could be beneficial for some individuals (by decreasing their risk of heart disease) but harmful for other individuals (by increasing their risk of hemorrhagic stroke) (1990, p. 79).

Unfortunately, *all three* of the preceding operational concepts can also be criticized for *excluding* some effects that many researchers regard as instances of chemical hormesis (such as curves that exhibit thresholds because of difficulties in measuring low-dose effects) and *including* some effects that are often considered to be non-hormetic (such as the effects of essential nutrients). On the one hand, Calabrese and Baldwin note that if the background level of a particular endpoint is particularly low or high, it may not be possible to observe inhibition or stimulation (respectively) of the endpoint that occurs at low doses. So, for example, if tumor incidence occurs relatively rarely in a particular population, a hormetic effect that decreases tumor incidence might result in a curve with a *threshold* below which no effect is observed rather than in a U-shaped dose-response curve. Calabrese and Baldwin suggest that effects of this sort should be considered hormetic, but all three preceding concepts of chemical hormesis could be criticized for inappropriately *excluding* such phenomena. On the other hand, essential nutrients, especially metals, produce U-shaped dose-response curves that involve low-dose stimulation and high-dose inhibition. Such phenomena are *included* in the scope of the three preceding concepts, but most researchers do not consider them to be instances of chemical hormesis (e.g., Davis and Svendsgaard 1990, p. 72).

Because of these difficulties involved in defining chemical hormesis operationally, mechanistic concepts of chemical hormesis may be more helpful for future researchers. A fourth concept, "overcompensation hormesis," can be defined as a biological response in which processes are stimulated to above-normal levels in an attempt to restore organismal homeostasis after it is altered by a toxic chemical (see figure 2). For example, the growth of

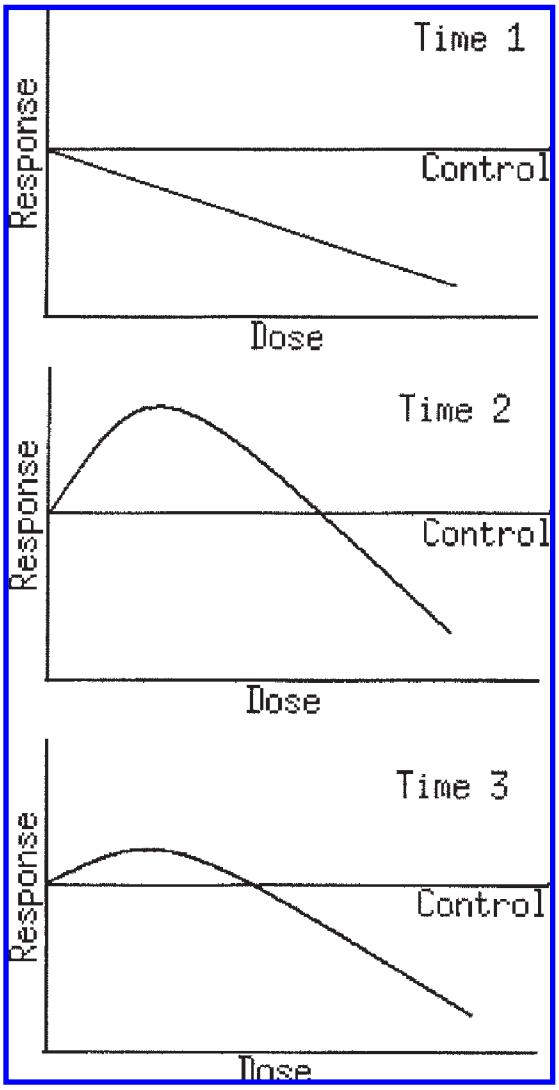

Figure 2. Example of the temporal dependence of the dose-response relationships characteristic of overcompensation hormesis.

peppermint plants is initially inhibited at all dose levels by treatment with the growth retardant phosphon, but after two to five weeks of treatment, the plants exposed to low doses of phosphon appear to overcompensate to this stress, because they grow faster than controls (Calabrese and Baldwin 1998*c,* pp. 354–355). Overcompensation hormesis, initially proposed by Anthony Stebbing, is the most widely accepted *mechanistic* concept of chemical hormesis. He suggests that hormetic effects on organism growth are caused by overcompensation to perturbations in homeostasis caused by toxic substances. The growth of organisms is monitored and controlled by feedback processes, and he suggests that it is evolutionarily advantageous for these feedback processes to respond to biological stressors by temporarily "overshooting" the return to homeostasis. This response prepares the organism for further disturbances, and the organism gradually returns to a normal state if it is not disrupted further (Stebbing 1997, pp. 3–9). According to Calabrese and Baldwin, the distinctive characteristics of overcompensation hormesis are *temporal:* overcompensation hormesis is unique in that a linear dose-response curve occurs shortly after administration of a toxin, but the curve becomes U-shaped (representing an overcompensation response at low dose levels) after the body's feedback mechanisms have time to respond (1998*c,* p. 354).

A fifth concept, "direct stimulation hormesis," can be defined as a biological response in which low doses of a chemical directly stimulate a particular endpoint but inhibit the same endpoint at higher doses. Such apparent direct stimulation has been observed on the fermentation rate in yeast exposed to arsenic, the rate of DNA synthesis in chick embryo cells exposed to zinc, the prostate weight of male mice exposed to diethylstilbestrol, and numerous other endpoints (Calabrese and Baldwin 1998*c,* p. 356). As mentioned in section I, this is the other broad type of chemical hormesis reported in Calabrese and Baldwin's literature search (1998*b*). Calabrese and Baldwin acknowledge, however, that this concept of chemical hormesis actually encompasses an array of mechanisms rather than one particular mechanism (1998*c,* p. 357). The stimulation could result from the enhancement of phenomena such as mitosis, cell wall/membrane permeability, hormone secretion, repair of genetic material, energy utilization, nutrient uptake, or enzyme synthesis. Numerous other mechanisms for "direct stimulation" hormesis revolve around the regulation of enzymatic reactions (1998*c,* p. 358). Because of this variability in underlying mechanisms, the dose-response curves for direct-stimulation hormesis were different, and much more varied, than the dose-response curves for overcompensation hormesis observed in Calabrese and Baldwin's study. Stimulatory effects varied from the level of overcompensation hormesis (around 150%) to at least 1000% of the control, and the hormetic dose

range varied from the level of overcompensation hormesis (around 10-fold) up to about 30 million-fold in the studies that Calabrese and Baldwin categorized as examples of "direct stimulation hormesis" (1998*c,* p. 356).

A sixth mechanistic concept is "multiple-effects hormesis," defined as a low-dose effect, opposite to that which occurs at higher doses, that is caused by multiple biological effects of a chemical influencing the same endpoint in different ways at different dose levels. Davis and Svendsgaard hint at this concept of chemical hormesis (1990, p. 77).[3] The effects of alcohol on human mortality appear to provide a good example of this concept of chemical hormesis. Alcohol stimulates levels of HDL cholesterol at low doses (thus lowering risk of mortality by heart disease), but this positive effect is offset at high doses because of other effects that increase cancer risk. Calabrese and Baldwin do not appear to favor this concept of chemical hormesis (personal communication). Nevertheless, it is possible that some apparent cases of "direct stimulation" hormesis are actually the result of multiple effects of chemicals. In fact, unless chemical "effects" are defined very precisely and directly, almost any U-shaped dose-response curve could be attributed to multiple effects of a chemical. Even the "overcompensation" response observed by Stebbing might be describable as an indirect, secondary effect of a chemical whose primary effect is the inhibition of an endpoint associated with growth.

None of these mechanisms, either alone or in combination, appears at present to be a completely satisfactory concept of chemical hormesis. First, the mechanisms are not precisely specified. The causal processes underlying direct stimulation hormesis are not understood. Thus, no criteria for distinguishing instances of direct-stimulation hormesis (or even overcompensation hormesis) from multiple effects of a single chemical have presently been propounded. Second, a concept based on any combination of these mechanisms is likely to exclude phenomena that some researchers would consider hormetic. Davis and Svendsgaard report a variety of such phenomena. The interactive effects of some metals may inhibit carcinogenesis and produce U-shaped dose-response curves on certain endpoints. U-shaped dose-response curves could result from the potential for organisms to adapt to chronic low-level exposures to a particular toxin. Finally, organisms have numerous compensatory and protective mechanisms that defend the body against stressors and that may produce

3. Although Davis and Svendsgaard touch on this concept, it has not been emphasized elsewhere in previous literature, but the validity of this mechanism was debated frequently at a recent conference ("Chemical and Radiation Hormesis," January 2000, at the University of Massachusetts, Amherst) on the evidence for chemical hormesis.

above-normal effects on certain endpoints, at least for a time (1990, pp. 77–78). Such mechanisms do not appear to represent instances of the three preceding concepts of chemical hormesis.

A seventh concept of chemical hormesis, "adaptive hormesis," may be distinguished on the basis of its genesis. It is a low dose biological effect, opposite to that which occurs at higher doses, that has developed as an adaptive response to biological stressors. For example, Calabrese and Baldwin argue that instances of overcompensation hormesis (such as the growth response of peppermint plants to phosphon) are likely produced by generalized adaptive strategies that have developed as a result of natural selection (1998*b,* p. VII-15). Such a genetic concept of chemical hormesis has great plausibility, especially in combination with other operational or mechanistic concepts of chemical hormesis, because it provides an evolutionary account that would explain the existence of hormetic effects. However, it appears inordinately difficult to provide *criteria* for determining cases of adaptive hormesis. Thus, despite the suggestion of Calabrese and Baldwin that instances of low-dose stimulation should be considered hormetic only if they are adaptive (1998*b,* p. VII-1), it is probably unreasonably stringent to demand that a particular effect be shown to have developed via adaptive processes before it can be regarded as an instance of chemical hormesis.

III. Ramifications of the Conceptual Clarification

If the preceding conceptual analysis of "chemical hormesis" is plausible, then at least three ramifications should be considered. First, this analysis supports moderate skepticism about the existence of chemical hormesis. This is an *epistemic* claim concerning the warrant provided by current evidence for chemical hormesis. The conceptual analysis provided in this paper highlights the fact that a number of distinct mechanisms could be involved in the production of "hormetic-looking" effects in certain contexts, and current evidence provides little information about the frequency and conditions under which any single mechanism is operative. It is still possible, of course, that future evidence will support the existence of a generalizable low-dose phenomenon to which the term "chemical hormesis" can be appended. The phenomenon that presently seems most likely to represent a unitary low-dose effect of toxic chemicals is the "overcompensation hormesis" observed by Stebbing and Calabrese and Baldwin. Nevertheless, this phenomenon may be confined to a circumscribed number of endpoints (e.g., growth) and may depend on carefully circumscribed conditions (e.g., a suboptimal environment) (Calabrese and Baldwin 1998*c,* p. 354; Vichi and Tritton 1989, p. 2679). Furthermore, even if this is a replicable phenomenon, current evidence does not confirm

how often this particular low-dose effect occurs relative to other low-dose effects of toxic chemicals. Therefore, even though Calabrese and Baldwin have pointed to a number of *sociological* factors that may have contributed to the past demise of the chemical hormesis hypothesis (1999*b,* p. 727; 2000*e,* p. 92), the *philosophy-of-science* analysis exhibited in this paper provides sufficient warrant for rejecting the chemical hormesis hypothesis at present.

The second ramification of the foregoing conceptual analysis is that the necessary and sufficient conditions for confirming the generalizability of chemical hormesis are more complex than previous research suggests. Given the multiplicity of concepts circulating in recent articles on chemical hormesis, it is necessary to specify the particular concept being studied and to provide evidence for the generalizability of that particular phenomenon. In Calabrese and Baldwin's literature search (Calabrese and Baldwin 1998*b*), their criteria were designed to uncover evidence of U-shaped dose-response curve hormesis.[4] However, they argued for the generalizability of the hormetic phenomenon not based on the frequency at which U-shaped dose-response curve hormesis was observed but rather based on the plausibility of the existence of mechanistic concepts of hormesis such as overcompensation and direct-stimulation. Unfortunately, they did not provide evidence for the frequency at which any of these concepts of chemical hormesis occurred relative to non-hormetic dose-response curves (Elliott 2000, pp. 181–185). Future research will need to specify concepts of chemical hormesis more carefully in order to warrant the acceptance of the hormesis hypothesis. As the introduction to this paper indicated, this should not be taken to imply that conceptual imprecision cannot play a productive role in scientific research; rather, it means only that conceptual clarification may prove valuable in certain cases at certain times.

The third ramification of the conceptual analysis in section II is that the implications of chemical hormesis for carcinogen risk assessment are unclear. The concept that has the clearest implications for risk assessment is "beneficial hormesis." I have already argued, however, that this is an impractical concept because it is very difficult to show that the beneficial effects of a particular chemical occur over an extended period of time, for most members of a population, without being outweighed by negative side effects. The necessary and sufficient conditions for showing that phe-

4. The criteria included the number of doses from each study that were below the NOEL (no-observed-effect level), whether or not the NOEL was determined in the study, the number of statistically significant doses that showed a low-dose response opposite of the high-dose response, the magnitude of response, and reproducibility of the data (1998*b,* p. III-4).

nomena corresponding to *other* concepts of chemical hormesis have significant implications for carcinogen risk assessment are difficult to provide. Consider one necessary condition as an example: evidence will be needed that hormetic effects occur with high frequency on endpoints that reflect *the entire process* of carcinogenesis (e.g., incidence of cancer-related illness or cancer-related mortality). This condition is necessary because a carcinogenic chemical could have a hormetic effect on one cancer-related endpoint (e.g., DNA repair enzyme activity) but have other short- or long-term side effects that increase the overall chance of suffering harm on more significant endpoints such as cancer-related illness or mortality (Elliott 2000, pp. 187–190). This point is closely related to Shrader-Frechette's claims (this issue, section 4) that it is questionable to infer, based on short-term studies of only a few biological endpoints, that beneficial radiation hormesis effects occur. If changes in the current default models of risk assessment are to be considered (e.g., eliminating the current assumption that there is no threshold for the harmful effects of carcinogens), sufficient evidence must exist that hormetic effects occur on endpoints that reflect the *entire process* of carcinogenesis (e.g., endpoints like cancer-related illness or mortality).

Unfortunately, evidence of this sort is not easy to marshal once specific concepts of chemical hormesis are carefully considered. Calabrese and Baldwin have noted that low-dose biological effects on endpoints such as cancer-related mortality are very difficult to determine, because they require the use of epidemiological studies (1998*b,* p. VIII-33). One reason for this difficulty is that these low-dose effects are typically small, so a very large sample size is needed in order to obtain statistically significant effects in an epidemiological study. Therefore, it will be very difficult to show that *operational* concepts such as U-shaped dose-response curve hormesis are applicable to the endpoints that are truly significant for risk assessment. *Mechanistic* concepts of hormesis appear to show more promise for impacting risk-assessment practice, because a mechanistic link could potentially be demonstrated between easily measured phenomena (such as an overcompensation response on certain endpoints) and effects on more significant endpoints such as cancer-related mortality. Unfortunately, the preceding conceptual clarification suggests that there may be so many different mechanisms involved in the production of hormetic-looking effects that it will be very difficult to relate all these different mechanistic phenomena with effects on endpoints that are important for risk assessment.

Nevertheless, the analysis provided in this paper suggests a positive project for future research concerning hormetic phenomena and their applicability to risk assessment. First, researchers should probably focus attention on several *specific mechanistic phenomena* and elucidate criteria for

distinguishing different mechanistic phenomena from one another. The "overcompensation hormesis" observed by Calabrese and Baldwin and Stebbing may constitute a particularly promising phenomenon for further research, because its temporal dependence provides a relatively straightforward operational means of distinguishing it from other low-dose phenomena. Second, experiments designed to provide statistical evidence for the *frequency* with which *particular chemicals* produce these *specific mechanistic phenomena* in specific *organisms* under specific *conditions* (e.g., suboptimal as opposed to optimal environments) will do much to increase the warrant for those specific hormetic phenomena.

Third, convincing arguments for some degree of *generalizability* of these phenomena might involve either elucidation of the physiological pathways associated with these specific phenomena or statistically supported evidence that these specific phenomena occur with high frequency in certain classes of organisms (e.g., plants) as a result of exposure to certain chemical classes (e.g., metal salts). Fourth, application of these phenomena to public policy will require evidence that the *interactive effects* of multiple toxic chemicals on these mechanistic phenomena will result in *long-term* beneficial low-dose effects on *endpoints that reflect the entire process of carcinogenesis.* Experiments designed to elucidate the likely interactive and long-term effects of chemicals on the physiological pathways shown to be associated with the hormetic phenomena, together with an evaluation of the relationship between these physiological pathways and endpoints that are significant for risk assessment (such as cancer-related mortality), might prove valuable in this context.

Conclusion

This paper argued for three theses concerning the epistemological warrant for the existence and generalizability of chemical hormesis. The first section of the paper argued that the different concepts of chemical hormesis employed by proponents and opponents of the hormetic hypothesis support different conclusions about the plausibility and generalizability of chemical hormesis. Section II analyzed seven concepts of chemical hormesis, arguing that each is unsatisfactory considering the state of present research. Finally, the last section argued that this conceptual analysis, which highlights the potentially diverse low-dose effects of toxic chemicals, suggests that chemical hormesis may not exist, that the necessary and sufficient conditions for confirming the generalizability of chemical hormesis are more complex than has been recognized formerly, and that the implications of chemical hormesis for carcinogen risk assessment are unclear. This analysis should contribute to ongoing scientific understanding of chemical hormesis and of its implications for public policy. It also

provides a case study supporting the positive role that philosophy-of-science approaches such as conceptual clarification can play in addressing scientific disputes, including disputes concerning policy-related science that might appear to be driven by social or political considerations.

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