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Introduction

Properly extrapolating the effects of toxic chemicals from high doses to low doses is an ongoing, important, and controversial issue among toxicologists, risk assessors, and managers. Most bioassays of chemicals involve a preponderance of high doses because the assays are designed to show statistically significant evidence for the carcinogenicity of a chemical.[1] When risk assessors and managers set exposure guidelines for such a chemical, they typically extrapolate its effects at low doses by making the assumption that its dose-response curve is linear in the low-dose region.[2] Recent research on the phenomenon of chemical hormesis may challenge this assumption.[3]

Hormesis is a positive biological response produced by extremely low doses of a biological stressor such as a toxic chemical or ionizing radiation. It is characterized by a U-shaped dose-response curve in which inhibitory effects are roughly proportional to dose above the no-observed-adverse-effect-level (NOAEL) but stimulatory effects are observed below the NOAEL until the dose drops to zero.[4] Although research supporting the generalizability of this phenomenon appears to contradict the assumption of linear dose-response curves used in current

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1 *See* Edward J. Calabrese & Linda A. Baldwin, Chemical Hormesis: Scientific Foundations, II.31 (1998).

2 *See* Edward J. Calabrese & Linda A. Baldwin, *Can the Concept of Hormesis Be Generalized to Carcinogenisis*, 28 Regulatory Toxicology and Pharmacology 230, 230 (1998).

3 *See* Calabrese & Baldwin, *supra* note 1, at VIII.1; *see also id.*

4 *See* Edward J. Calabrese & Linda A. Baldwin, *Hormesis as a Biological Hypothesis*, 106 Envtl. Health Persp. 357 (Supp. 1998).

risk-assessment practice, the validity and importance of this research is currently under discussion.[5]

Edward Calabrese and Linda Baldwin (hereafter C and B) recently completed one of the most thorough examinations of the evidence for chemical hormesis.[6] They carried out an extensive literature search with a quantitative methodology designed to uncover evidence for chemical hormesis in previous toxicology studies.[7] They concluded that chemical hormesis is both a widely generalizable phenomenon[8] and that "the concept of hormesis (i.e., low-dose stimulation/high-dose inhibition) is counter to the cancer risk assessment practices by U.S. regulatory agencies such as the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Hazard Association (OSHA) which assume that cancer risk is linear in the low-dose area."[9] These claims are likely to be particularly influential because Calabrese is a well-known figure in the study of the toxicological effects of low-level chemical exposures.[10] An earlier paper by Calabrese et al. has been widely cited in support of the existence of chemical hormesis,[11] and his recent work with Linda

5 *See e.g.*, Ortwin Renn, *Implications of the Hormesis Hypothesis for Risk Perception and Communication*, 17 Hum. and Exper. Toxicol. 431 (1998).

6 *See* ARD Stebbing, *Hormesis — The Stimulation of Growth by Low Levels of Inhibitors*, 22 Sci. Total Env't 213 (1982); *see also* J. Michael Davis & David J. Svendsgaard, *U-Shaped Dose-Response Curves: Their Occurrence and Implications for Risk Assessment*, 30 J. of Toxicol. and Env't Health 71 (1990); *see also* Edward J. Calabrese et al., *The Occurrence of Chemically Induced Hormesis*, 52 Health Physics 531 (1987).

7 *See* Calabrese & Baldwin, *supra* note 1, at II.31; *see also* Calabrese & Baldwin, *supra* note 4; *see also* Edward J. Calabrese & Linda A. Baldwin, *The Dose Determines the Stimulation (and Poison): Development of a Chemical Hormesis Database*, 16 Int. J. Toxicol. 545 (1997); *see also* Edward J. Calabrese & Linda A. Baldwin, *A Quantitatively-Based Methodology for the Evaluation of Chemical Hormesis*, 3 Hum. and Ecol. Risk Assessment 545 (1997).

8 *See* Calabrese & Baldwin, *supra* note 1, at 4.

9 *Id.* at VIII-1; *see also* Calabrese & Baldwin, *supra* note 2, at 230.

10 Calabrese is the chairman of the Biological Effects of Low Level Exposures advisory board, a group of scientists organized to develop a better understanding of biological responses to low doses of chemical and physical agents. He is editor of the journal Biological Effects of Low Level Exposures, and he has organized several conferences related to the hypothesis of hormesis. *See e.g.*, K.A. Skov, *Perspectives on the Adaptive Response from Studies on the Response to Low Radiation Doses (or to Cisplatin) in Mammalian Cells*, 18 Hum. Exp. Toxicol. 450 (1999).

11 *See* Calabrese et al., *supra* note 6 (this article has been cited over 40 times); *see e.g.*, Harold Boxenbaum et al., *Hormesis, Gompertz Functions, and Risk*

Baldwin is cited by those who are evaluating the implications of chemical hormesis for risk assessment and management.[12]

Furthermore, a number of recent articles made claims similar to those of C and B. For example, in a recent paper, Justin Teeguarden et al. claimed that the attention that chemical hormesis has received 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."[13]

In a paper evaluating the implications of chemical hormesis for quantitative risk assessment, Sielken and Stevenson made a number of proposals concerning the risk assessment of toxic chemicals. They proposed that low-dose risk characterization will need to reflect the likelihood of beneficial effects at a dose and that sufficiently small dose levels are not likely to have any adverse effects.[14] Sielken and Stevenson state that the communication of uncertainty will need to be expanded to include lower bounds as well as upper bounds "to reflect not only how harmful a dose might be but also how beneficial some doses might be."[15] They also suggest that "greater explicit use of expert judgment and weight-of-evidence based distributional analyses will be needed to reflect more of the available dose-response information."[16] The authors agree that these changes are long overdue.

In addition, the abstract of another recent paper by Johnson and Bruunsgaard reports that the implications of such non-linearity [hormesis] are such that governmental regulatory activities and other

Assessment, 19 Drug Metabolism Rev. 195 (1988); *see also* C.T. De Rosa et al., *Public Health Implications of Environmental Exposures*, 106 Env. Health Persp. 369 (Supp. 1998).

12 *See e.g.*, Justin G. Teeguarden et al., *Implications of Hormesis on the Bioassay and Hazard Assessment of Chemical Carcinogens*, 17 Hum. Exp. Toxicol. 254 (1998); Jeffery A. Foran, *Regulatory Implications of Hormesis*, 17 Hum. Exp. Toxicol. 441 (1998), *see also* Renn, *supra* note 5; *see also* Skov, *supra* note 10.

13 Teeguarden, *supra* note 12, at 257.

14 *See* Robert L. Sielken, Jr. & Donald E. Stevenson, *Some Implications for Quantitative Risk Assessment if Hormesis Exists*, 17 Hum. Exp. Toxicol. 259 (1998).

15 *Id.*

16 *Id.*

areas of public health administration will be affected to a large extent once hormesis is widely recognized.[17] Thus, the implications with regard to environmental intervention and subsequent regulatory decisions will profoundly affect the political process.[18]

According to those authors, chemical hormesis has significant implications for risk assessment and regulation. So far, however, governmental agencies are slow to accept implications of chemical hormesis for risk assessment and management. As Renn reports, "regulatory agencies prefer to ignore this phenomenon as not yet proven or to deem it irrelevant for pursuing their public mandate."[19] Two EPA scientists recently claimed that "those who wish to advance the consideration of biological effects of low-level exposures (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."[20] Thus, there are indications that a public policy conflict is developing with regard to the risk-assessment implications of chemical hormesis. Furthermore, it might appear that the conflict is characterized by a growing body of scientific research that stands in opposition to the unwarranted "inertia" of governmental regulatory agencies and of society at large.

This article sets forth the proposition that the "inertia" of government agencies and of society may reflect a very reasonable and cautious perspective toward current research on chemical hormesis. This perspective is justified by at least two sets of considerations. Foran points to both social factors (e.g., political commitment to reduce pollution to levels that are as low as reasonably achievable) and scientific/technical factors (e.g., the need to quantify hormetic effects) that contribute to people's cautious reactions to recent research.[21] Articles on risk perception and communication further explore some of the social factors that relate to chemical hormesis, but those articles

17 *See* Thomas E. Johnson & Helle Bruunsgaard, *Implications of Hormesis for Biomedical Aging Research*, 17 Hum. Exp. Toxicol. 263 (1998).

18 *See id.*

19 Renn, *supra* note 5, at 431.

20 J. Michael Davis & William H. Farland, *Biological Effects of Low-level Exposures: A Perspective from U.S. EPA Scientists*, 106 Env. Health Persp. 380 (1998).

21 *See* Foran, *supra* note 12.

tend to bracket or assume the generalizability of hormesis and its scientific implications for policy.[22] Thus, the social factors partially explain government policy, but they do not fully justify policy decisions. The justifiability of the positions taken by government agencies depends a great deal on the evaluation of the second set of factors mentioned above: scientific and technical considerations. Surprisingly, the literature includes few evaluations of this sort.[23]

With these considerations in mind, this article highlights and clarifies some of the scientific and technical factors that may justify the cautious perspective of governmental agencies toward the risk-assessment implications of chemical hormesis. C and B have performed a very extensive and high profile study that has (to my knowledge) not yet been evaluated, so I will proceed by examining their recent work as a case study. Because a number of authors are making claims similar to C and B, the scientific and technical issues highlighted in this study should be broadly applicable to current discussions of chemical hormesis. The case study consists of three parts: (1) an evaluation of C and B's scientific evidence for the generalizability of chemical hormesis; (2) an evaluation of C and B's argument that carcinogenesis is a hormetic endpoint; and (3) an evaluation of C and B's claim that hormesis runs counter to current governmental risk assessment practices. I will conclude with some suggestions concerning the ongoing research that ought to be pursued if chemical hormesis is to be applied to risk-assessment policy.

Generalizability of Hormesis

C and B present one of their central conclusions in the executive summary of their report: "In summary, hormesis appears to be highly generalizable, not only with respect to the descriptive nature of the dose-response phenomenon, but also with respect to species, chemical, and biological endpoint."[24] That conclusion could be misleading

22 *See e.g.*, Paul Slovic, *If Hormesis Exists . . . : Implications for Risk Perception and Communication*, 17 Hum. Exp. Toxicol. 439 (1998); *see also* Renn, *supra* note 5.

23 I am not aware of any critical examinations of C and B's recent research on hormesis. Davis & Farland, *supra* note 20 and Foran, *supra* note 12, are among the few articles that have considered *scientific/technical* issues associated with the application of chemical hormesis to risk assessment.

24 Calabrese & Baldwin, *supra* note 1, at 4.

because it confidently affirms that hormesis is generalizable without noting two important limitations of the study: (a) this was that a weight-of-evidence study designed to look only for confirming instances of hormesis; and (b) the implications that C and B reported for the low-dose extrapolation of dose-response curves were based on an examination of only a small minority of the articles found in their literature search (less than 600 out of 8,500).[25]

Some background information is necessary to understand those points. C and B's evaluation of the hypothesis of hormesis started with a series of literature searches using key words related to hormesis. After eliminating database replications of articles, the researchers were left with about 8,500 articles. Then, they performed a manual review of these studies, yielding about 585 that they deemed "potentially relevant."[26] Unfortunately, they do not explain what exactly they mean by the expression "potentially relevant."[27] Contextually, it appears that they considered "potentially relevant" articles to be those that might provide evidence of chemical hormesis. After collecting those articles, they designed, a priori, qualitative evaluation criteria based on factors such as number of doses, dose range, reproducibility, and statistical significance to determine the evidence for hormetic effects in the 585 articles. Based on those criteria, evidence of hormesis (ranging from low to high degrees of evidence) was found in about 350 studies.[28] Finally, the 350 studies were reevaluated using more objective, quantitative criteria, and the studies were once again classified according to degree of evidence for a hormetic dose-response curve.[29]

As mentioned above, this study design was limited since it was not designed to systematically examine the effects of toxic chemicals at low doses, but rather to collect a variety of cases in which chemicals may have exhibited hormetic effects. Since the researchers structured this study to look only for positive instances of hormesis, it is uncertain how many studies exist that provide evidence for linear dose-response curves

25 *See id.* at II.1.

26 *Id.* at II.1, II.10-11.

27 *Id.*; *see also* Calabrese & Baldwin, *supra* note 4.

28 *See id.* at II.1.

29 *See id.* at III.10-13.

in the low-dose region. Francis Bacon recorded the dangers of looking at evidence supporting only one side of a scientific hypothesis, and his concerns are still instructive today. "The human understanding when it has once adopted an opinion . . . draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects and despises, or else by some distinction sets aside and rejects . . . [so that] the authority of its former conclusions may remain inviolate."[30]

C and B supported their claim that hormesis is generalizable by showing that hormesis occurred in a wide variety of contexts.[31] Yet this finding probably does not mean as much as it might initially appear. At present, researchers have not yet systematically examined the mechanisms that produce chemical hormesis.[32] Thus, researchers are very limited in their ability to explain its appearance or to predict when it will or will not occur. Despite the fact that hormesis has been observed in a number of species at a variety of endpoints with many different chemicals, it could be that these hormetic effects consistently occur only under certain conditions (e.g., when an organism is in an optimal state of health and in an optimal environment). Thus, hormesis may be generalizable in one sense, but the reader of C and B's study cannot confidently affirm the significance of this generalizability for extrapolating the low-dose region of dose-response curves.

In a sense, the second limitation of C and B's study is just a specific example of the first limitation. It is uncertain whether some of the 7,915 studies that turned up in the literature search, and that were considered "irrelevant" to the hormetic hormesis, might actually serve as counterexamples to C and B's claim concerning the generalizability of hormesis. Their manual review was apparently designed to isolate only articles that supported the hypothesis of hormesis. Thus, it is possible that some of the roughly 7,900 rejected articles had a significant number of low doses and doses below the NOAEL and would have provided evidence for a linear dose-response curve under the conditions given in the articles. Considering that C and B did not elaborate on the characteristics of the numerous studies that they

30 Francis Bacon, The New Organon, 50 (1960).

31 *See* Calabrese & Baldwin, *supra* note 4, at 359-60.

32 *See id.* at 360-61.

rejected, it is uncertain how much significance to place in the roughly 350 studies (less than 5% of the 8,500 studies that contained key words related to hormesis) that appeared to show some evidence for the occurrence of hormesis. Once again, we recognize that C and B provided examples of hormetic dose-response curves, but the implications of these curves for the extrapolation of dose-response curves in general is not clear.

Notably, C and B provide an explanation for the general lack of toxicology studies demonstrating chemical hormesis. They explain that the studies that would most likely exhibit hormetic effects (i.e., studies with a number of doses below the NOAEL) are infrequently performed since risk assessors want to determine the dose-response curves for high doses of chemicals. C and B estimate that about 500,000 toxicology studies have been performed in this century, but only about 10,000 contain six or more doses, about 1,000 have three or more doses below the NOAEL, and about 900 have doses in the range in which hormetic effects would be expected to occur.[33] Despite the limitations in their claim that chemical hormesis is widely generalizable, they do explain that the lack of articles that support the hypothesis of hormesis is most likely due to the lack of appropriate studies that are performed.

The primary difficulty with that defense is that C and B only provide a possible explanation for the lack of studies that support hormesis. If there are about 900 articles that could be expected to display evidence for or against hormesis, their claim would be supported more convincingly by an examination of those 900 articles, reporting the number of articles that displayed positive evidence of hormesis, the number of articles that displayed evidence that hormesis did not occur, and a report of factors that could be used to explain or predict the presence or absence of chemical hormesis. As the evidence now stands, C and B only show that hormesis occurred in a variety of cases and that the lack of additional studies demonstrating hormesis may be due to limitations in study design. It is possible that the lack of studies demonstrating chemical hormesis reflects the presence of unknown factors that determine whether a chemical displays a hormetic or linear dose-response curve under varying conditions.

33 Calabrese & Baldwin, *supra* note 1, at II.31; *see also* Calabrese & Baldwin, *supra* note 4, at 360-61.

If the limitations mentioned here are legitimate, it is important to understand their implications. C and B's study had several goals. One of their goals was to further the respectability of the hypothesis of chemical hormesis, and the limitations mentioned here do not seriously detract from that particular goal. Nevertheless, C and B (along with the other researchers cited in the introduction) also wish to apply the study's claims about the generalizability of hormesis to risk assessment.[34] This effort could be seriously misleading if the limitations mentioned here are not taken into account. It would be unwise to factor the hypothesis of chemical hormesis into risk-assessment policy without recognizing that C and B's evidence for the generalizability of chemical hormesis does not provide systematic information about the conditions under which hormetic dose-response curves might be expected to occur. At this point, it would be helpful if a research group performed an analytic research project that would make and test predictions about the mechanisms, chemicals, and conditions that are likely to result in hormetic effects.

Carcinogenesis as a Hormetic Endpoint

Thus far, this paper raises concerns regarding the evidence that C and B's study provides for chemical hormesis. The rest of this paper focuses more specifically on the risk-assessment implications of their study. One of their stated goals was to explore the implications of chemical hormesis for risk-assessment practices.[35] In chapter VIII of their study, they argued two main points: (1) that the process of carcinogenesis is a hormetic endpoint; and (2) that this implies that federal policies for risk assessment are inadequate. The following discussion evaluates their claim that carcinogenesis is a hormetic endpoint. Then I will evaluate the implications of this claim for risk-assessment policy.

C and B's claim that "the recognition that hormetic responses are widely generalizable with respect to chemical class, animal model, gender and biological endpoint suggests that the process of carcinogenesis should likewise be an endpoint where hormetic responses

34 *See* Calabrese & Baldwin, *supra* note 1.

35 *See id.*; *see also* Calabrese & Baldwin, *supra* note 2.

could be anticipated."[36] Before I further examine that argument, it is worth considering whether the process of carcinogenesis can be coherently referred to as an endpoint. In general, biological endpoints are a phenomena that can be quantitatively measured (e.g., longevity, growth, or enzyme activity). Processes are interactive developments that take place over a period of time and are not necessarily conducive to quantitative measurement. Although there are a number of endpoints related to some aspect of carcinogenesis to which C and B refer (e.g., DNA repair enzyme activity, damage to DNA, and cell division), it is not clear that the complex process of carcinogenesis as a whole is an endpoint that can be quantitatively measured. With this in mind, I suggest that C and B could make their claims about hormetic effects on the process of carcinogenesis more coherent by referring to hormetic effects on a quantifiable endpoint that can partially represent or correlate with the process of carcinogenesis. Two possible endpoints might be cancer-related deaths or incidences of cancer-related illness. For example, one may interpret C and B as claiming that high levels of exposure to carcinogenic chemicals correlate with statistically significant incidences of cancer-related illness, but extremely low levels of exposure to these same chemicals may correlate with incidences of cancer-related illness that lie below the level of controls.

This analysis may seem to be a case of linguistic or philosophical hair-splitting, but it serves two important purposes. First, it clarifies the exact positive effects (e.g., reduction in cancer-related illness) that a hormetic chemical is supposed to produce. Secondly, it minimizes the potential for sidestepping the issue being discussed. Referring to the process of carcinogenesis as an endpoint implies that a chemical could have a single, straightforward effect on this process. In actuality, carcinogenesis is a complex process that might be affected in a multiplicity of ways by a single chemical, and C and B are trying to argue that this multiplicity of effects can "boil down" to one overall positive effect. By noting that we are looking at endpoints representing the overall results of a complex process, we can better distinguish these endpoints from "simpler" endpoints that represent one aspect of carcinogenesis and that may not be affected by as many factors.

36 Calabrese & Baldwin, *supra* note 1, at VIII.1; *see also* Calabrese & Baldwin, *supra* note 2, at 230.

With this in mind, I return to C and B's suggestion that chemicals could have hormetic effects on the process of carcinogenesis. I am translating this suggestion into a more coherent claim that certain chemicals could have a hormetic effect on endpoints such as incidence of cancer-related illness that are related to the process of carcinogenesis as a whole. C and B supported that claim by looking at almost 20 studies in which carcinogens had a hormetic effect on individual endpoints associated with one of three aspects of carcinogenesis: initiation, promotion, or tumor development. The studies involved the effects of carcinogens on such phenomena as DNA repair enzyme activity, damage to DNA, cell division in the stomach and kidney, hyperplasia of the urinary bladder, and bladder tumor development.[37] Through those studies, they concluded by suggesting that hormetic responses for "cancer endpoints" in general (apparently including the process/endpoint of carcinogenesis) are highly generalizable.[38]

This argument must be examined. C and B looked at endpoints related to some aspect of carcinogenesis (e.g., damage to DNA) and argued that some studies show hormetic effects on those endpoints. C and B are trying to show that endpoints related to the overall process of carcinogenesis (e.g., incidence of cancer-related illness) are likely to have hormetic dose-response curves. Thus, this conclusion is based on the critical assumption that hormetic effects on endpoints associated with the process of carcinogenesis as a whole can be defended by pointing to hormetic effects on endpoints associated with some aspect of carcinogenesis. That assumption initially appears plausible in C and B's study because they refer to the process of carcinogenesis as an endpoint, and they do not make careful distinctions between different sorts of carcinogenic endpoints. As noted above, they claim, "[t]hat hormetic responses occurred with such a wide range of cancer endpoints argues that the phenomenon is highly generalizable."[39] My previous analysis has clarified, however, that endpoints related to the process of carcinogenesis ought to be distinguished from endpoints associated with some aspect of carcinogenesis. Endpoints associated with the

37 *See* Calabrese & Baldwin, *supra* note 1, at VIII-2-19; *see also* Calabrese & Baldwin, *supra* note 2, at 230-36.

38 *See* Calabrese & Baldwin, *supra* note 1, at VIII.34.

39 *Id.* at VIII.34.

whole process may be effected in many ways by a single chemical, whereas the same chemical is likely to have a more unitary effect on an endpoint associated with one aspect of carcinogenesis. It is troubling that C and B did not argue for the validity of their assumption.

In fact, there are at least two reasons that the assumption (namely, that the hormetic nature of endpoints related to carcinogenesis as a whole can be defended by showing hormetic effects endpoints associated with some aspect of carcinogenesis) is doubtful. First of all, as a matter of pure logic, this assumption is very similar to the fallacy of composition. When this fallacy is committed, properties of the parts of an entity are transferred to the entity as a whole. For example, by assuming that the entire U.S. government would work efficiently if every employee of the government worked efficiently. This would be an invalid inference if there were so few government employees that the government as a whole could not get work done efficiently even though each individual employee worked efficiently. Similarly, it is possible that low doses of a carcinogen beneficially effect one particular carcinogenic endpoint while damaging other endpoints and contributing to an overall propensity for cancer-related illness.

Despite the logical problems with C and B's assumption, a priori possibility exists that the hormetic nature of endpoints related to some aspect of carcinogenesis might correlate with a hormetic effect on endpoints associated with carcinogenesis as a whole. Nevertheless, there are empirical and logical reasons to doubt this assumption. Davis and Farland note that toxic chemicals may have a variety of effects at any particular dose level. [40] Thus, some effects may be beneficial at the same time that others are harmful.[41] An example of such multiple effects is found earlier in C and B's paper. C and B found 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."[42]

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40 See Davis & Farland, *supra* note 20, at 380.

41 *See id.*

42 Calabrese & Baldwin, *supra* note 1, at II.5.

Furthermore, the multiple and combined effects of toxic chemicals are especially noticeable when these effects are considered with respect to the complex process of carcinogenesis. As Yamasaki reports:[43]

> Since carcinogenesis is a multistage process, and each stage is influenced by a variety of endogenous and exogenous factors [1,2], estimation of the risk presented by a single chemical compound may not adequately indicate the overall risk of the entire carcinogenic process . . . the activity of initiating agents can only be assessed when promoting agents are applied, and the activity of promoting agents can only be estimated when initiating agents have been used. Therefore, it is inevitable that the dose-response of initiating agents is influenced by tumor-promoting agents, and the dose-response of tumor-promoting agents is influenced by the presence of initiating agents.

With these considerations in mind, it appears unwise to expect hormetic effects on endpoints associated with the complex process of carcinogenesis until C and B's assumption is explicitly defended.

One could defend C and B by pointing out that they marshaled the best possible evidence for their claim considering the difficulties of dealing with extremely low levels of chemicals. It would be nearly impossible to do an epidemiological study in which individuals were exposed to sub-inhibitory amounts of carcinogens for the purpose of observing statistically significant reductions in cancer rates.[44] Thus, C and B have done "the next best thing;" they have looked for hormetic effects at the endpoints at which particular carcinogens are known to contribute to the development of cancer. If a chemical has a positive effect on that particular endpoint, it may be trifling to suggest that the chemical could have some other effect on the process of carcinogenesis through more complicated, interactive mechanisms. In other words, I may be asking the impossible by asking them to provide a detailed defense of their assumption, but their assumption has a reasonable likelihood of being true even though it cannot be defended in full.

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43 Hiroshi Yamasaki, *Multistage Carcinogenesis: Implications for Risk Estimation*, 7 Cancer and Metastasis Reviews 5, 11 (1988).

44 *See* Calabrese & Baldwin, *supra* note 1, at VIII.33.

This debate can be clarified by maintaining focus on what has and what has not been shown in C and B's study. C and B were wise to introduce their chapter on carcinogenesis by claiming that the presence of hormetic effects on a variety of endpoints merely suggests that endpoints associated with the process of carcinogenesis as a whole should exhibit hormetic effects.[45] I think that the observation of hormetic effects on endpoints associated with aspects of carcinogenesis suggests the possibility of hormetic effects on endpoints associated with carcinogenesis as a whole. Yet, this suggestion should spur further research. Since it is not confirmed that endpoints associated with the whole carcinogenic process exhibit hormetic dose-response curve, one must weigh the plausibility of this assumption against the knowledge of complications. Some chemicals affect one endpoint positively and other endpoints negatively. Endpoints associated with the whole process of carcinogenesis are affected by a combination of factors, and a particular chemical might impact some of these factors positively while impacting other factors negatively. Finally, endpoints associated with the process of carcinogenesis reflect long-term developments that may exhibit different effects from short-term endpoints associated with some aspect of carcinogenesis. Thus, C and B's research is exciting and suggestive, but the application of their conclusions about carcinogenesis to risk-assessment policy appears premature.

Implications for Risk Assessment and Management

Assuming that the process of carcinogenesis proved to be a generalizable hormetic endpoint, would this imply that federal policies for risk assessment are inadequate? As mentioned earlier, C and B claim that "[t]he concept of hormesis is counter to the cancer risk assessment practices by U.S. regulatory agencies such as the EPA, FDA, and OSHA which assume that cancer risk is linear in the low dose area."[46] This probably should not be taken as a central conclusion of their report; it is a summary statement that introduces the twenty studies demonstrating hormetic effects on individual carcinogenic endpoints. Nonetheless, this statement makes a host of assumptions, and it is important to recognize these assumed auxiliary claims if one is to gain a

45 *See id.* at VIII.1.

46 *Id.* at VIII.1; *see also* Calabrese & Baldwin, *supra* note 2, at 230.

satisfactory understanding of the scientific and technical issues involved in applying chemical hormesis to risk-assessment policy.

Davis and Farland point out three reasons that the generalizability of chemical hormesis may not have significant implications for risk-assessment policy. First, as previously noted, they claim that toxic chemicals frequently have multiple effects, some of which might be hormetic at a particular dose and others of which could be harmful. Secondly, they note that the EPA must consider particularly sensitive subpopulations when they formulate their guidelines. Thus, both the average person and the member of a sensitive subpopulation would have to experience hormetic effects if a change in policy were to be warranted.[47] It should also be noted that the variation of hormetic effects among members of a population might be much more dramatic than the variation of typical toxic effects. Under normal circumstances, toxins affect those who are young, elderly, or pregnant more severely than they affect others. Furthermore, hormetic effects might vary even more sensitively based on an organism's stress, disease-state, genetic makeup, or exposure to other environmental factors.[48] Next, Davis and Farlan identified that hormetic effects in carefully-controlled laboratory settings may not mean much in the real world if humans are already exposed to background levels of chemicals that exceed the NOAEL.[49] In sum, the claim that hormesis runs counter to current risk-assessment practices assumes three auxiliary claims: (1) hormetic effects of toxic chemicals are the only relevant effect that the chemicals have; (2) there is a dose range at which both sensitive and non-sensitive members of the population could experience hormetic effects from chemicals; and (3) humans are not already exposed to dose levels that surpass the chemicals' hormetic dose ranges.

Additionally, there are at least two other auxiliary claims that C and B are forced to assume if they claim that chemical hormesis runs counter to risk-assessment policy. First, Foran points out that risk assessors must consider the concurrent effects of toxic chemicals. If several hormetic chemicals act via the same mechanism, it must be

47 *See* Davis & Farland, *supra* note 20, at 380.

48 *See* Foran, *supra* note 12, at 442.

49 *See* Davis & Farland, *supra* note 20, at 380.

determined whether the combined hormetic effects are synergistic or antagonistic.[50] For example, it is possible to imagine a scenario where several carcinogenic chemicals in the environment affect the endpoint of DNA mutations. Even if one toxic chemical was present in sufficiently low doses to stimulate an over-corrective, positive response, the presence of several of these toxic chemicals might be sufficient to "swamp" the body's corrective responses and produce a net harmful amount of DNA mutation. Thus, humans might be exposed to a very carcinogenic environment even though each of the toxic items in the environment would not be individually harmful. Besides considering the joint effects of several hormetic chemicals, risk assessors would also need to consider the combination of hormetic effects of some chemicals and toxic effects of other chemicals.[51]

Finally, another auxiliary claim is that risk assessors must consider the difference between short-term effects on single endpoints and long-term effects on whole organisms. It would not be surprising if some hormetic effects were beneficial in the short term but harmful in the long term. For example, C and B argue in their paper that hormesis should be "viewed within the context of a counteractive response to perturbations in homeostasis."[52] One would expect a priori that even if counteractive responses to perturbations in homeostasis had positive short-term effects on an individual endpoint, they might "wear down" the organism as a whole and result in negative impacts on the organism as a whole in the long term. In fact, I have already provided a quote from C and B demonstrating that the stimulation of detoxifying enzyme levels in larvae can be a short-term hormetic effect that has negative long-term effects on the whole organism.[53] Thus, C and B are also relying on the auxiliary claims that the concurrent effects of hormetic chemicals with other chemicals yield a net hormetic effect and that short-term, single endpoint hormetic effects can carry over into long-term hormetic effects on whole organisms.

C and B could defend the claim that they oversimplified the implications of hormesis for risk-assessment policy by responding that

50 *See* Foran, *supra* note 12, at 441.

51 *See id.* at 442.

52 Calabrese & Baldwin, *supra* note 1, at 3.

53 *See id.* at II-5.

they were merely making a summary generalization and that the auxiliary claims necessary to establish the conflict between hormesis and risk assessment policy are defensible. For example, C and B examined a study that presented the effects of caffeic acid on cell division during a rat's entire lifetime which pointed to hormetic effects.[54] That hormetic effect would presumably satisfy the auxiliary condition that a hormetic effect on one endpoint ought to carry over to long-term hormetic effects on the whole organism. Furthermore, Sielken and Stevenson suggest that the existence of chemical hormesis would imply that risk uncertainty characterizations should incorporate expert judgments. Therefore, some might suggest that the uncertainties involved in these auxiliary claims could be bridged by expert judgment.[55] Thus, researchers such as C and B may be gradually arriving at sufficient knowledge about chemical hormesis that they and other experts could develop some informed judgments about reasonable risk-assessment implications.

The problem with these five auxiliary claims is that, while possibly defensible in certain cases, they have not been systematically defended in C and B's study. They did not mention whether most of the studies in chapter VIII of their report covered the organisms' entire typical lifespans.[56] The studies do not address whether all human subpopulations would share hormetic effects at certain dose levels or whether those dose levels are already part of humans' background exposure. As for the possibility that expert judgments might alleviate some of these difficulties, Kristin Shrader-Frechette argued that in cases in which experts are forced to rely on a number of estimates, models, and heuristic judgmental strategies, the public may be just as qualified as the experts to determine appropriate policy for ethically-laden decisions.[57] The lack of systematic evidence for these five significant and largely unexplored auxiliary claims should be taken as an indication that experts do not have enough solid information to make more

54 *See id.* at VIII-10.

55 *See* Sielken & Stevenson, *supra* note 14, at 262.

56 *See* Calabrese & Baldwin, *supra* note 1, at VIII; *see also* Calabrese & Baldwin, *supra* note 2.

57 *See* Kristin Shrader-Frechette, *Evaluating the Expertise of Experts*, 6 Risk 118 (1995).

reasonable conclusions about the implications of chemical hormesis for risk-assessment policy than the general public.

It is possible to conceive of a somewhat different objection to the issues to which I have expressed concern. Perhaps I am partially confusing the risk management of hormetic chemicals with the risk assessment of hormetic chemicals. Risk assessment is "the characterization of the potential adverse health effects of human exposures to environmental hazards."[58] Risk management, on the other hand, is "the process of evaluating alternative regulatory actions and selecting among them."[59] It could be argued that some of the complicating factors that this paper addresses (especially a chemical's combined environmental effects with other chemicals) are only relevant to risk management, so C and B's claims about risk-assessment policy do not rely on all of these auxiliary claims.

Although I agree that the distinction between risk assessment and risk management is an important distinction in principle, it is probably not applicable in this case. If low doses of numerous hormetic chemicals were accepted in the environment, the risk assessment for a particular chemical X could not be based on the dose-response curve for exposure to that chemical alone. Many chemicals are legislated individually, so it would be unwise to assume that all other chemicals would be regulated in such a way that their combined effects with X would be satisfactory. For all practical purposes, if the hypothesis of hormesis were accepted, the applicable dose-response curve for X would need to be based on the effects of X at particular doses in conjunction with the small doses of all the other chemicals that would be present in the environment. Thus, if a number of chemicals that exhibited hormetic effects could actually produce negative effects when present together, it would appear that even acceptance of the claim that hormesis contradicts risk-assessment practice depends on a defense of the auxiliary claims that I have mentioned.

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58 Committee on the Institutional Means for Assessment of Risks to Public Health, **Risk Assessment in the Federal Government: Managing the Process** 18 (1983).

59 *Id.*

Conclusions

As I noted at the beginning of this article, the scientific and technical issues discussed in this case study should be generally applicable to discussions of chemical hormesis and its implications for risk assessment. I chose to use C and B's recent studies of chemical hormesis as a case study because they performed some of the most comprehensive work to date on this topic and as such, their research is likely to be particularly influential. My concerns should not be taken as an indication that C and B have done poor work. Rather, my goal is to illustrate that the best work in the field still necessitates further investigations concerning: (1) the generalizability of hormesis; (2) the hormetic nature of endpoints associated with the total process of carcinogenesis; and (3) the implications of hormesis for risk assessment. C and B's literature search legitimized further studies of hormesis by bringing attention to numerous toxicology studies in which hormetic effects can now be recognized after-the-fact. However, even as they noted, a literature search of this sort has strengths and weaknesses. The benefit of this after-the-fact evaluation is that hormetic effects were less likely to be produced by researcher bias. The disadvantage is that the original studies were not optimally designed for the purpose of studying chemical hormesis.[60] As future researchers respond to C and B's work and pursue studies that are specifically designed to examine chemical hormesis, hopefully they will address the concerns that are developed in this paper.

I would suggest that all future research concerning the generalizability of hormesis should take an analytic approach rather than a weight-of-evidence approach. C and B's approach was sufficient for bringing chemical hormesis to people's attention, but an analytic approach would isolate factors that explain and predict hormetic effects and provide more systematic information about the low-dose region of dose-response curves. It is this sort of systematic, explanatory, and predictive information that can ground risk-assessment policy. It is also important that further research is developed to prove if and when endpoints associated with the complex process of carcinogenesis may display hormetic dose-response curves. This is due to the weaknesses of epidemiological studies in showing the small positive effects that are

60 *See* Calabrese & Baldwin, *supra* note 1, at VIII-32-33.

characteristic of hormesis.[61] It may be necessary to develop new and creative means to show when the hormetic effects of a chemical on an endpoint, associated with some aspect of carcinogenesis, can be used to predict a hormetic effect on an endpoint associated with the overall process of carcinogenesis. It is important that researchers and policy makers maintain the distinction between these two very different sorts of "carcinogenic endpoints." Finally, the third section of this paper provides a compilation of auxiliary claims that ought to be considered if chemical hormesis is to be applied to current risk-assessment practice. These five claims suggest that experts may not be qualified to affirm conflicts between hormesis and risk-assessment policy until further research is accomplished. Hopefully, the arguments developed in this article will improve and spur this future research, considering that C and B's findings "should provide a strong incentive for further development of this area of inquiry given its potential to enhance understanding of responses at realistic levels of exposures."[62]

61 *See* Calabrese & Baldwin, *supra* note 2, at 230.

62 *Id.* at 240.