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Hormesis: A New Religion?

Cook and Calabrese (2006) make inaccurate claims about our perspective on hormesis (Thayer et al. 2005). They define hormesis as “low-dose stimulation and high-dose inhibition,” declaring “beneficial/harmful effects should not be part of the definition, but reserved to subsequent evaluation. . . .” Yet, they advocate higher permissible environmental levels of hazardous agents based on purported health benefits. Cook and Calabrese promote changing the way carcinogens are regulated to accommodate hormesis, recognizing that this “would result in cancer risk assessment values about 100- to 200-fold higher than currently employed” (Calabrese and Cook 2005). Previously, Calabrese and Baldwin (2003a) stated, “agencies will need to accept the possibility (actually, the likelihood) that toxic substances, even the most highly toxic (e.g., cadmium, lead, mercury, dioxin, PCBs, etc.) can cause beneficial effects at low doses.”

We are concerned that changing health policies to permit higher exposures based on alleged benefits would be harmful, particularly to susceptible subgroups and individuals exposed to mixtures (Thayer et al. 2005). Instead Cook and Calabrese (2006) suggest that policy decision making “may tend to bring various subgroups in the population together to debate one group’s health benefit against another group’s health risk.” To pit one group against another is absurd. Health-protective default assumptions that are used to compensate for uncertainties should not be dismissed based on untested propositions that likely incur greater risks.

Contrary to statements made by Cook and Calabrese (2006), in our article (Thayer et al. 2005) we never claimed that hormetic responses are rare. Rather, we argued that hormesis should not be assumed as universal. In fact, we have published on nonmonotonic dose responses in biological systems (Kohn and Melnick 2002; Welshons et al. 2003). We argue against the assumption that “an exposure limit in the range of the maximum stimulation could promote appreciable benefits in public health” for the general population (Cook and Calabrese 2006). Yet, we fully support addressing non-monotonic dose–response relationships in risk assessments.

Further, we never claimed that “comprehensive mechanistic knowledge is necessary” before making a public health decision. In

fact, we have a history of arguing the contrary. Indeed, if this standard were operating today, we might still be debating the dangers of tobacco smoke and benzene, among many others. Calabrese appears to overstate the frequency of hormetic dose–response curves. Some responses considered “stimulatory” are not, such as decreased interleukin-2 release, blood pressure, memory, and prolactin level (Calabrese and Baldwin 2003b). His hormesis database contains U- or J-shaped curves where the low dose “stimulation” is actually decreased compared to control values (Calabrese and Baldwin 2001). There should be some mechanistic indication of what specifically is being stimulated (and inhibited at higher doses) before considering a curve hormetic. Otherwise, the empirical observations of Calabrese and colleagues simply reflect nonmonotonic dose responses.

The quote we used from the BEIR VII (National Research Council 2005) that draws attention to the lack of evidence of a health benefit from low doses of ionizing radiation was not misleading; Kaiser (2005) also reported that the National Research Council dismissed “the hypothesis that tiny amounts of [ionizing] radiation are harmless or even beneficial,” noting that cancer risk increases proportionally with exposure. In contrast, Calabrese and Cook (2005) claimed that all or most carcinogens have a hormetic dose(s) at which tumors will be decreased. This is contrary to what we know about the carcinogenicity of chemicals and radiation.

Labeling a dose response as hormetic to justify higher exposures and claimed benefits for the general population without providing scientific evidence is counter to public-health protective assumptions. For example, cadmium has been touted as a hormetic agent with benefits (Calabrese and Baldwin 2003) because low doses are associated with decreases in testicular tumors in rats. However, Waalkes et al. (1997, 1988) reported increases in prostate tumors within the hormetic dose range for testicular tumors. In our article (Thayer et al. 2005), we emphasized the latter, whereas it was seemingly ignored by Calabrese and Baldwin (2003), because cadmium is a human carcinogen and includes associations with cancer of the prostate and other organs [National Toxicology Program (NTP) 2004]. In addition, differential susceptibility must be addressed because it is well established that cancer and other health risks from

ionizing radiation, some chemotherapeutics, and passive tobacco smoke are much greater for those exposed *in utero* or as children. We should not allow another tragedy such as the one caused by diethylstilbestrol.

Disease prevention strategies should not rely on higher environmental exposures to known toxicants (e.g., cadmium, lead, mercury, dioxin, polychlorinated biphenyls). Setting environmental exposure limits based on ranges of maximum stimulation (i.e., equated with postulated hormetic benefits) is a totally unjustified public health policy that would impose greater involuntary risks on sizable segments of the population.

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Suggested Corrections to the Farm Family Exposure Study

Acquavella et al. (2004) reported glyphosate exposure analyses from the Farm Family Exposure Study (FFES) using biomonitoring. The authors “analyzed urine samples for creatinine to assess the completeness of daily samples,” but inadvertently used as “the normal range” 0.8–1.4 mg/dL and 0.5–1.1 mg/dL for males and females, respectively, which are the normal ranges of serum creatinine [National Institutes of Health (NIH) 2003]. The NIH normal values for urine creatinine are 24-hr total excretion values ranging from “500 mg/day to 2000 mg/day” (NIH 2006). Thus, Acquavella et al. (2004) needed to compare the 24-hr creatinine collection (urine creatinine concentration \times urine volume) to each individual’s normative value of daily creatinine excretion based on age, sex, and body surface area (Cockcroft and Gault 1976).

Acquavella et al. (2004) also did not correct for the initial conditions. Of 47 farmers, 7 had 24-hr urinary glyphosate concentrations above the minimum detectable value of 1 ppb immediately before the start of their application. Such a farmer who had zero exposure during the monitored application would have excreted glyphosate over the following 4-day collection period in an amount estimable from the measured individual excretion rates. For a truly unexposed applicator to be shown to have a dosage statistically similar to zero, this estimated total 4-day excretion with zero exposure must be subtracted from the 4-day collection value.

In addition, Acquavella et al. (2004) evaluated one application per family and called it only a “potential limitation,” without realizing that this may vitiate their study. If all 47 FFES subjects with complete data had an identical exposure distribution, any single applicator sampled 47 different times would have an expectation of presenting exposure data with a statistically similar mean and variance as the FFES 47 sampled only once each. Therefore Acquavella et al. (2004) cannot reject the possibility that all 47 applicators have a similar exposure

distribution by taking only one sample from each. This is because an applicator’s pesticide exposure is a stochastic process (accidents happen) that varies wildly from day to day, unlike the applicator’s weight that is a relatively constant process that barely varies from day to day. Therefore a single measured exposure provides no statistical information for estimating the applicator’s mean exposure over any time period other than the day measured. Furthermore, farmers’ pesticide exposures are not results of a stationary process, (defined as a time series in which the mean and variance of measured exposures, over a sufficiently long period from time 1 to time 2, are constants independent of choice for time 1). In an earlier study, we (Mage et al. 2000) successfully modeled the risk of accidental high pesticide exposure events in the Agricultural Health Study population as decreasing with the increasing lifetime number of application days. As one might expect, we showed that as an applicator gains experience, the risk of high exposure decreases. Therefore differences in lifetime experience of the FFES applicators prior to sampling introduce another variance component into the analysis.

In conclusion, Acquavella et al. (2004) treated a single sample at the end of a non-stationary time series—with declining mean and finite variance—as if it were actually the true mean value of a stationary process with zero variance. I recommend that Acquavella et al. (2004) consider revising their analyses by correcting properly for incomplete urine collection, correcting for the initial condition of prior glyphosate exposure, and adjusting for the experience of the applicator (lifetime number of application days) as an explanatory variable.

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The Farm Family Exposure Study: Acquavella et al. Respond

We thank Mage for his comments. In our article on glyphosate in the Farm Family Exposure Study (FFES) (Acquavella et al. 2004), we used 24-hr urinary creatinine to assess the completeness of daily samples over 5 days for the 48 participating farmers. We erred by summarizing the results as micrograms per deciliter instead of micrograms per day. Using an expected daily excretion of 566 μ g/day as the lower end of the normal range (Bingham et al. 1988; Forman 2003), only four 24-hr urine samples over 5 days were below that lower limit. Therefore, the completeness of urine collection for the applicators was exceptional. Further details of the urine collection and our assessment of completeness can be found in a related article (Baker et al. 2005).

Mage criticizes us for not subtracting preapplication urine values in our assessment of systemic dose related to on-study applications. Indeed, seven of the applicators had detectable glyphosate in their urine on the day before their on-study application (Acquavella et al. 2004). Values were 1.1, 2.6, 3.9, 5.3, 8.3, 9.8, and 15.4 ppb. We intentionally did not correct for these initial values for two reasons. First, from an epidemiologic and public health standpoint, it is instructive to know the total dose for farmers during and after an application, which, for example, could then be compared to levels of toxicologic significance. Second, the overestimate caused by this practice is trivial for glyphosate in both an absolute and relative sense. Consider that glyphosate has a U.S. Environmental Protection Agency (EPA) reference dose of 2 mg/kg/day (U.S. EPA 1999), and the highest systemic dose we estimated in our study was 0.004 mg/kg/day. The requested corrections would be to the ten thousandths of a milligram per kilogram per day or less.

Last, Mage calls the fact that we only evaluated one application per farm family a limitation that may vitiate our study. That is a strong indictment for a study that comprehensively assessed exposure for farm families related to a single application of three pesticides to an extent not seen before. We agree that characterizing intraperson variation in absorbed pesticide dose over several seasons would provide valuable information, but that was not the objective of the FFES. Nevertheless, Mage’s claim that we cannot reject the possibility that all 47 applicators have the same exposure distribution is refuted by our observations that absorbed dose was related to specific practices (e.g., not wearing gloves) and by similar findings

in the literature that practices dictate absorbed dose (e.g., Arbuckle et al. 2002).

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Risk Assessment and Epidemiologic Evidence in Environmental Health Science

There appears to be a serious conceptual error about the role of the various environmental health sciences in Kundi's otherwise interesting and informative commentary on "Causality and the Interpretation of Epidemiologic Evidence" (Kundi 2006). This error is exemplified in his next-to-last paragraph:

Most risk assessment procedures demand that for chronic diseases such as cancer there must be epidemiologic evidence before an extrinsic agent can be ascribed a hazardous potential for human health.

In fact, it is solely toxicologic evidence that is used for the overwhelming majority of agents to which a "hazardous potential for

human health" is ascribed. I am unaware of any risk assessment process that requires epidemiology to recognize hazardous potential for human health.

Perhaps Kundi (2006) meant that there must be epidemiologic evidence for a chemical to achieve the level of a known or proven cause of a hazard to human health. However, the misunderstanding in the above quote permeates his commentary.

As Kundi (2006) correctly recognized, it is better to prevent the introduction or use of agents that would cause adverse effects eventually identifiable in an epidemiologic study. Such prevention is primarily the role of predictive toxicology. Yet, as Kundi stated in his abstract, his recommended dialogue approach to "the potential for disease causation" starts with epidemiology.

Kundi (2006) concluded that the principle that every disease has a cause is metaphysical, but still has heuristic value. He appears to mean that the principle of causation helps us explore the potential that environmental factors cause human disease—and that we do so by developing models, such as risk assessment, that approximate reality without achieving certainty. However, a risk assessment, or any other model, that must depend on epidemiologic evidence to recognize the potential for disease causation represents a failure of environmental health science.

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Risk Assessment and Epidemiologic Evidence: Kundi Responds

I appreciate Goldstein's remarks about the role of epidemiology in risk assessment of environmental hazards and the opportunity to clarify my standpoint.

With reference to the International Agency for Research on Cancer's classification scheme of agents for their carcinogenicity in humans and other schemes such as that of the U.S. Environmental Protection Agency (EPA), Pitot and Dragan (2001) stated in *Casarett and Doull's Toxicology*:

In spite of the limitations of these classifications, an agent cannot be proven to be carcinogenic for the human unless substantial epidemiologic evidence supporting such a claim is available.

Although this statement refers to carcinoma and not to the broader class of chronic diseases, it seems to be very close to my statement (Kundi 2006) that Goldstein criticizes. However, Goldstein particularly emphasizes that I may have meant that "there must be epidemiologic evidence for a chemical to achieve the level of a known or proven cause of a hazard to human health."

The reader may have noticed that I never used the term "proven" (Kundi 2006), and I deliberately did not. In my opinion we cannot reach the level of a proven cause. Our knowledge is always incomplete; although we may be quite sure about a factor causing a disease, it may turn out to be actually unrelated. Using toxicologic evidence, we may conjecture that an agent has a potential to cause human chronic disease, but we need further evidence—in most cases epidemiologic evidence—to establish a causal relationship between the agent and a chronic disease in humans. (I make a conceptual difference between "establishing" and "proving," the latter defined as "establishing truth," which can only be done for analytical statements.)

My statement that Goldstein criticizes was misleading insofar as it seems to indicate that we have to start from epidemiologic evidence to ascribe an agent a hazardous potential for human health. In many cases first information on a potential hazard will stem from routine toxicologic testing. The last paragraphs of my commentary (Kundi 2006) were intended to give an outlook to future developments that may provide answers to the question of causation of chronic diseases in a more rapid fashion. From this context it should be clear that risk assessment was addressed with respect to the causal role of an agent. Therefore, a slight modification of the statement above is appropriate: An agent cannot be established to cause a chronic human disease unless supporting epidemiologic evidence is available. Among other improvements, comprehensive utilization of modern molecular biological methods integrated into epidemiologic designs may provide such evidence at an early stage of the disease.

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