

## Hormesis and the Law\*

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Professor Cross concludes that "the evidence for hormesis is sufficiently strong that the government should alter its default presumption of linear dose-response models."(1) While we do not doubt that hormetic effects have been proven for some substances and some end points, we believe, for several reasons, that Professor Cross's recommendation is unwarranted at this time.

Before turning to our reasons for rejecting Professor Cross's proposal, a definitional note is in order. Hormesis is "the stimulatory effect of subinhibitory concentrations of any toxic substance on any organism."(2) Put simply, substances that exhibit hormetic effects may be beneficial to health at low doses but harmful at high doses. Small amounts of vitamin A, for example, are required for human survival, but large amounts are toxic; either exposure extreme, in other words, can be fatal.

Many of the substances that have been shown to have a j-shaped dose-response curve - a curve consistent with a hormetic effect - are naturally occurring substances that, like vitamin A, are required for human survival. They are also substances, the human response to which has been optimized over thousands of years of evolution. No case has been made, in the literature on hormesis or elsewhere, showing that the synthetic chemicals implicated by Professor Cross's analysis - chemicals such as benzene, PCBs, and pesticides - are biologically necessary for our survival. Indeed, humans survived for millennia without ingesting benzene or PCBs or DDT.

In addition, not all (or even most) of the beneficial consequences of toxic substances can be characterized as hormetic effects. A hormetic effect is a direct, biological effect of a substance on an organism; it is not an indirect effect of a substance on human health. The use of DDT can, for example, sometimes prevent larger risks from malaria than the risks from cancer it creates, but this does not mean that DDT has a *hormetic* effect. Hormesis is not synonymous with the presence of risk tradeoffs. Professor Cross errs in implying that it is. For example, he asserts that chloroform has a hormetic effect because chlorine is used to purify our drinking water.(1) By overstating the breadth of the concept of hormesis, Professor Cross threatens to confuse the research on hormesis with the burgeoning literature on risk tradeoffs.(3) This literature is quite problematic enough without this new potential for error.(4)

Definitional complexities aside, our first objection to Professor Cross's proposal for eliminating the linear, no-threshold default model in regulatory analysis of carcinogens arises from our belief that the assumptions underlying hormesis as an alternative regulatory construct are no more compelling than the assumptions underlying the linear, no-threshold model of carcinogenesis. Professor Edward Calabrese and Linda Baldwin's recent review of the literature on the hormetic effects of carcinogens is instructive in this regard. The animal studies cited in that review used populations of rodents that suffered from high spontaneous or induced background tumor incidence; indeed, the background tumor rate for most of the rodents used in these studies was 50 percent.(5) It is not at all clear that one can extrapolate from such findings to a rodent or human population with a lower background incidence of tumors. One will recognize, in this example, a familiar conundrum: whether and how to extrapolate from findings in one animal or human population to conclusions about a different animal or human population. This is, of course, the conundrum that has led to the default linear, no-threshold model of carcinogenesis that Professor Cross criticizes. There is solid scientific research confirming the hypothesis that some carcinogens exhibit a linear, no-threshold dose-response curve.(6) Our objective here is not, however, to prove once and for all which curve - the j-shaped, hormetic curve, or the linear, no-threshold curve - most precisely describes biological reality. Our point, rather, is that *both* curves require extrapolation into areas where our scientific knowledge is at best imperfect.

Even if the currently limited findings on the hormetic effects of carcinogens were clearly generalizable to all animals and humans, Professor Cross's proposal to eliminate the linear, no-threshold default assumption used in regulatory analyses of carcinogens would nevertheless suffer from several problems. All of these problems stem from the same basic fact: in each study showing the existence of hormetic effects, the *beneficial* portion of these effects occurs in a very tiny sliver of the dose-response curve.(5) For several reasons, the minuteness of the concentrations involved in creating a beneficial effect counsels against elimination of the linear, no-threshold default assumption in regulatory analysis.

First, the beneficial effects of hazardous substances appear to occur, if at all, only at extremely low levels, and thus it is possible, perhaps even likely, that most regulatory programs are currently operating on the portion of the dose-response curve that leads to harmful effects. Only one statutory provision requires the complete elimination of carcinogenic substances; this provision is the infamous "Delaney Clause" of the Federal Food, Drug, and Cosmetic Act. The reach of even this one provision has been

dramatically curtailed.(7) Because all other statutes allow some exposure to carcinogenic substances, it may be that currently allowed exposures are above the range of hormetic effects. The research on hormetic effects is simply beside the point when this is the case. Professor Cross suggests, counterintuitively, that even in this situation hormetic effects are relevant because they might justify *more stringent* regulation,(1) but this argument assumes that the governing standard is a cost-benefit standard (a relatively rare standard in the regulation of carcinogens).

A second implication of the size of the portion of the dose-response curve exhibiting beneficial effects is that regulation will have a hard, perhaps impossible, time accomplishing the kind of fine-grained calibrations necessary to capture the beneficial effects of toxic substances without causing the harmful ones. Not only will research into the biological effects of carcinogens become even more complex and expensive than it already is (requiring, among other things, vastly increased numbers of experimental animals), but the methods for control of hazardous substances will need to become more fine-grained as well. Technologies designed to control hazardous substances typically result in "lumpy" controls, that is, they reduce pollution in quite large rather than small increments. It would be exceedingly difficult to calibrate pollution controls so precisely as to mitigate only that amount of pollution that exists above the threshold of beneficial hormetic effects. Certainly, it will be difficult to identify that threshold. In fact, the impossibility of identifying such thresholds is precisely what led to the creation of the regulatory "margins of safety" that Professor Cross criticizes.(1)

Finally, even if it were possible to identify the precise point at which toxic substances ceased to have a harmful effect and began to have a beneficial effect, it would assuredly not be the case that the level at which this occurred would be the same for all human populations. Certainly some human populations - especially those populations already vulnerable to illness due to age, illness, gender, or other characteristics - would still be experiencing adverse effects at levels at which other populations were beginning to enjoy health benefits. Professor Cross can elide the normative and practical difficulties created by this situation only by ignoring the differential susceptibilities of human populations to illness and premature death.

Of course it would be wonderful if it turned out that the chemicals we have been discharging and discarding for decades actually helped some humans avoid serious illnesses. And of course credible evidence that this wondrous situation exists should affect the regulation of these chemicals. The question, in our view, is who should bear the burden of proving that this situation indeed prevails with respect to a given chemical. We believe that the

government's current default rule places the burden where it should be: on those who would challenge the assumption of a linear, no-threshold dose-response curve. Let business interests, with their greater resources and superior access to information about the effects of the hazardous substances they produce, bear the burden of showing that those same substances are good for us.

We close with a simple thought experiment. Imagine that Post or Kellogg's asked the Food and Drug Administration to allow it to include very small amounts of dioxin in its breakfast cereal in response to findings suggesting that dioxin reduces tumor incidence in rats.<sup>(5)</sup> Would it be appropriate for the FDA to allow this action based on existing studies of hormetic effects? More to the point, would it be appropriate for the FDA to place the burden of proof on those objecting to the inclusion of dioxin in breakfast cereal? It seems to us that, if anything, the case for controlled, informed, voluntary ingestion of substances with putative hormetic effects is stronger than the case for uncontrolled, uninformed, involuntary exposure to such substances, and yet we would find it surprising if anyone urged that the burden of proof be shifted to those opposing the cereal makers' proposal in the thought experiment we have posed.

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