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The Cost of Reducing Scientific Uncertainty Concerning Hormesis: A Commentary

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The cost of reducing scientific uncertainty concerning hormesis: a commentary on Professor Cross's paper

VR Walker

Professor Cross provides a preliminary examination of how the regulatory structure of the United States might deal with the reality of hormetic effects. My comments focus on only one aspect of that issue: the scientific uncertainty in fact-finding about hormetic effects, and the cost of reducing such uncertainty to an acceptable level. Under federal law in the United States, administrative actions are generally unlawful if a court finds them to be “arbitrary or capricious”.¹ In practice, this means that in order for a rulemaking, licensing decision, or administrative order to be lawful, there must be a rational basis for the action. The administrative action must be based on a consideration of all the relevant factors, and there must be an understandable, coherent rationale for the decision that is justified under the agency's statutory mandate.^{2–4} My main points in these comments are that fact-finding about hormetic effects must be warranted by the available evidence, that the cost of reducing scientific uncertainty about hormetic effects in particular cases is substantial and sometimes prohibitive, and that the science policies needed to fill the residual gaps in scientific information must continue to be justified within the confines of the relevant statutory mandates.

Regulatory policy in the United States has recognized the possibility of hormetic curves for decades, although indirectly. A hormetic dose-response curve such as the one in Professor Cross's Fig. 4 is a special case of a dose-response curve in which there is a threshold for adverse effects. Point E_0 (at which relative risk equals 1.0) is the threshold point at which adverse effects begin to occur as exposure increases. Regulatory agencies have seldom had reason to determine the shape of the dose-response curve below the threshold. Any agency that is not allowed to balance benefits against risks has no reason to determine whether hormetic benefits occur. For any agency that is permitted to take benefits into account, the expected benefits of determining the shape of the subthreshold portion of the dose-response curve must be

weighed against the costs. I will suggest that the cost of finding the shape of the dose-response curve below the threshold is usually substantial, and may be prohibitive.

The shape of the hormetic portion of any particular dose-response curve is a question of empirical fact, to be determined only on the basis of adequate scientific evidence. Figure 1 is a modified version of Professor Cross's Fig. 4. The existence of a hormetic effect means that the tipping point E_t , “where [according to Professor Cross] human health is maximized,” is not identical to E_0 . I have inserted two gray error bars or confidence intervals (and question marks at the ends of each bar) to indicate that there is a range of relative risk values that is consistent with any given data. Due to sampling uncertainty, any given set of data is not statistically significant for rejecting a population relative risk anywhere within the confidence interval. That is, the subthreshold portion of the curve could take many different shapes, consistent with any given data.

Attempts to reduce sampling uncertainty about the shape of the subthreshold curve are attempts to reduce the width of the confidence intervals around the data points. In general, the width of a confidence interval for relative risk is a function of the sample size — increasing the size of the sample decreases the width of the interval, other factors being equal.⁵ At a minimum, the confidence interval has to be narrow enough to allow a warranted finding of a difference between test groups and controls. For example, in Figure 1, if the confidence interval around point E_t is so wide that it includes a relative risk of 1.0, we would not be warranted in finding any hormetic effect at all. This is because a relative risk equal to 1.0 is evidence that there is no difference in effect rate between the test and control groups. In addition, in order to determine the shape of the subthreshold curve, studies would have to have test groups at a sufficient number of different exposure levels below the threshold, in order to have enough data points to determine the locations of E_0 and E_t , and the

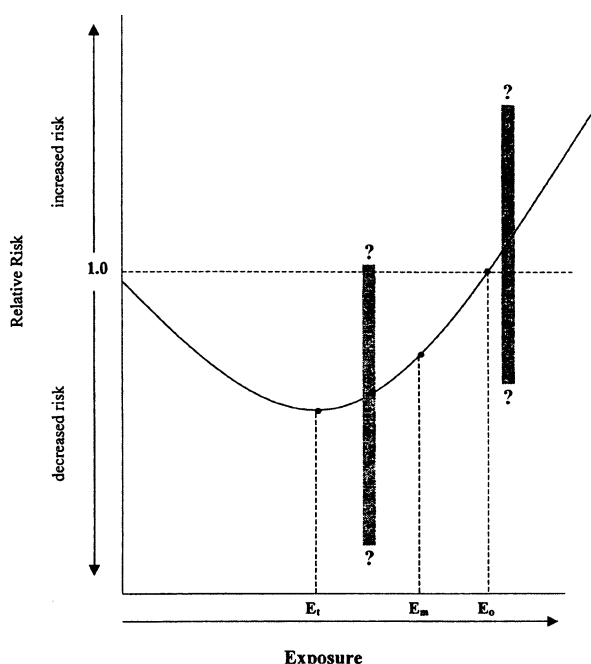


Figure 1

shape of the curve below E_o . For each exposure level, there would have to be enough test animals to narrow the confidence interval appropriately. Therefore, for chemical agents with thresholds, there may be a substantial cost of determining that the chemical also has a hormetic effect.

In the case of carcinogenic agents, the cost of generating similar data would be prohibitive and seldom, if ever, economically feasible. We seldom have evidence even of a carcinogen's threshold, due to a combination of factors. The first is sample size, as mentioned above. The second is the rarity of the adverse event, relative to background rates (the rates in controls). The carcinogenic effects we are looking for may be relatively rare, especially at low exposures, and sample sizes would have to be large in order to find that the lack of a statistically significant difference between test groups and controls is not simply due to chance. Third, carcinogenicity studies normally must be conducted over the whole lifetime of the test animals. Therefore, even using strains of animals bred to reduce the background rate of cancer, the cost of an adequate study to identify a threshold of a carcinogen is prohibitive. *A fortiori*, generating the data needed to establish the location of E_t and the shape of the curve below the threshold would hardly ever be economically feasible.

All agencies, even those with statutory mandates only to protect health or safety, must conduct their own data-generating activities within limited budgets. Moreover, all agencies should weigh the costs

and benefits to society before they require any private parties to generate data. This means that incurring or imposing the costs of generating scientific information about the subthreshold portion of dose-response curves must be justified on a case-by-case and program-by-program basis. I have elsewhere catalogued different types of scientific uncertainty, in addition to sampling uncertainty.⁶ But even considering only sampling uncertainty, the cost of reducing such uncertainty to acceptable levels is substantial, and perhaps prohibitive.

When the cost of generating adequate data about hormetic effects is too high, can agencies proceed without such data? The lack of scientific data about an important step in the risk or benefit assessment process is the primary rationale for instituting science policies.⁷ If risk assessments could actually be performed on the basis of adequate evidence at a reasonable cost, there would be far less reason to have science policies at all. But when agencies adopt science policies to guide fact-finding, those policies must be justified by reasoning based on statutory objectives, or else the resulting fact-finding will fail to satisfy the "arbitrary or capricious" standard. Statutes enacted for the purpose of protecting health and safety provide a rationale for adopting conservative science policies. On the other hand, if a less protective science policy is to be adopted, the agency would need to articulate a policy objective that weighs against health and safety and that justifies some particular stopping point short of conservative protection. Those agencies that are allowed by law to weigh benefits, risks, and costs still need a policy justification for adopting science policies that are less than conservative. Useful rationales have been hard to come by.

Finally, I concur with Professor Cross that the possibility of hormetic effects brings up a management issue similar to the Food Quality Protection Act's requirement that cumulative exposures be taken into account. Even if someone were to generate sufficient scientific evidence to warrant a finding that there is a hormetic effect from a low dose of some compound C, that finding alone does not answer the question of how such an optimal dose should be administered or obtained. That dose could be ingested as a dietary supplement or through normal diet, could be dermally absorbed from a cream, could be ingested through water, or could be inhaled. Any of these exposures could be either voluntary or without specific consent. One legal problem, as Professor Cross notes, is that our array of health, safety, and environmental laws would have to be rewritten in order to address this

management question coherently. For historical reasons, current laws are organized primarily around route of exposure (water, air, etc.) or instrument of exposure (food, drug, etc.). Massive bureaucracies and political coalitions are entrenched within those jurisdictional boundaries, and have an interest in defending them. Another problem is that very few current laws provide any economic

incentive even to generate data about hormetic effects, as a requirement for marketing a product or conducting an activity. Until some rational restructuring of those laws is achieved, very few agencies or private parties will have any economic incentive to fund the generation of the needed data on hormesis, even where the generation of that data is feasible.

References

- 1 Administrative Procedure Act, 5 U.S.C. Sections 551–557, 706.
- 2 *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 1971.
- 3 *Motor Vehicle Manufacturers Association v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 1983.
- 4 Aman AC Jr., Mayton WT. *Administrative Law*. West Publishing Co., St. Paul, MN, 1993.
- 5 Lilienfeld AM, Lilienfeld DE. *Foundations of Epidemiology*. Oxford University Press, New York, Oxford, 1980.
- 6 Walker VR. The siren songs of science: toward a taxonomy of scientific uncertainty for decisionmakers. *Connecticut Law Rev* 1991; 23: 567–626.
- 7 Walker VR. Keeping the WTO from becoming the “world trans-science organization”: scientific uncertainty, science policy, and factfinding in the growth hormones dispute. *Cornell Int Law J* 1998; 31: 251–320.