Harvard
Center for
Risk
Analysis

*Using Decision Sciences to
Promote Public Health*

OCTOBER 2004

Volume 12
Issue 4

Risk in Perspective

REGULATION OF HORMETIC SUBSTANCES

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"Whether hormesis implies a loosening or strengthening of regulations depends on the incremental cost of controlling exposure."

Introduction

Environmental-health regulations of substances which may cause cancer, and of some other toxicants (e.g., airborne fine particulate matter), are based on the idea that a substance that might cause harm at high levels of exposure will cause harm at any exposure. For these regulations the linear no-threshold (LNT) model of the relationship between exposure and harm is standard. This model assumes that the probability of an adverse effect is proportional to exposure over the entire range and that there is no threshold below which the probability of harm vanishes. Under the LNT model, the only level of exposure at which there is no probability of harm is zero.

An alternative hypothesis, hormesis, describes the situation in which a substance is harmful at high exposure but beneficial at low exposure. There are many examples of substances with hormetic properties, such as medicines, and minerals which are essential nutrients at low levels but toxic at high exposure. Proponents of this alternative hypothesis suggest that hormesis provides a more realistic description of experimental exposure-response data for many substances than does the LNT model.

This essay examines the implications of the hormetic hypothesis for environmental regulation from an economic perspective. The economic perspective takes as its goal the maximization of human welfare, including human health. Contrary to the commonly held assumption that hormesis suggests that environmental regulations should be relaxed, the hormetic model can support either more or less stringent regulation than the LNT model, depending on the incremental cost of controlling exposure.

Exposure-Response Relationships under LNT and Hormetic Models

Exposure-response functions for the LNT and hormetic models are illustrated in Figure 1. The LNT model assumes the probability of harm is proportional to the exposure. This relationship is illustrated by the straight line. The hormetic model assumes that low-level exposures are beneficial, while higher exposures are harmful. This produces the J-shaped response curve.

The two curves are constructed so that they agree at two points - at zero exposure, where the substance causes no response, and at a high level of exposure, H. This is appropriate because the most reliable — and perhaps the only — data showing effects on humans or laboratory animals are usually for relatively high exposure levels. Both the LNT and hormetic exposure-response functions must be consistent with these observations and can

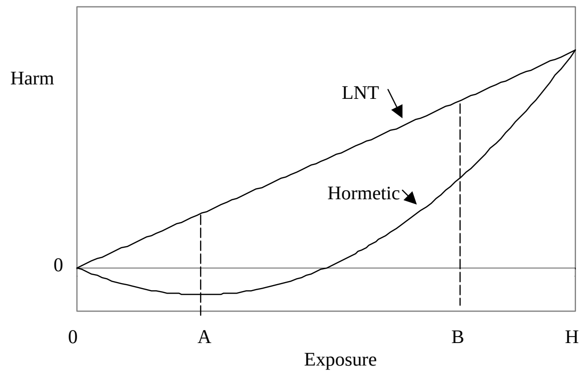

Figure 1 – LNT and hormetic exposure-response functions

differ only in the low-exposure region where any effects on humans cannot be reliably measured. Between these two points, the probability of harm is smaller (and perhaps less than zero) under the hormetic model than under the LNT model.

Identifying Optimal Regulatory Targets

From an economic perspective, the goal of regulation is to minimize total harm, which is equal to the sum of the monetary value of the harm from exposure plus the costs of controlling that exposure. Control costs are defined as the opportunity cost of the resources consumed (or behavioral changes required) to reduce exposure in the least costly manner. Countervailing risks caused by actions to reduce exposure, like side effects of medications, can also be considered as part of the control cost.

Figure 2 introduces the control costs under the LNT model. The monetary value of the harm from exposure is taken to be proportional to the harm, which would be appropriate if the harm is a small probability of cancer or other adverse health effect.

Without regulation, exposure is assumed to be equal to the relatively high level, H. As

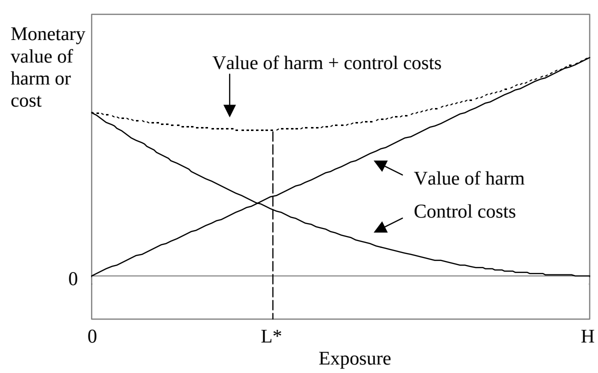

Figure 2 – Optimal regulation under the LNT model

exposure is reduced below H (moving from right to left on the graph), control costs are assumed to increase at an increasing rate. The assumption that additional reductions in exposure become increasingly costly is reasonable since one would initially adopt the most cost-effective methods for reducing exposure (i.e., those that cost the least per unit of exposure reduction), resorting to less cost-effective methods only as needed to attain the final increments of exposure reduction.

As exposure is reduced below H, the monetary value of the harm falls, but the control costs increase. The optimal regulatory target is the point that minimizes the sum of harm plus control costs, denoted L*. This point can also be identified as the point at which the incremental cost of tighter controls (the negative of the slope of the control-cost curve) is equal to the incremental benefit of tighter controls (the slope of the exposure-harm curve).

Figure 3 depicts the case under the hormetic model, including the same control costs as in Figure 2. Because the harm at any level of exposure between zero and H is smaller under the hormetic model than under the LNT model, the curve showing the sum of the monetary value of the harm plus control costs is lower in Figure 3 than in Figure 2. However, the lowest point on this curve, T*, where the sum of the harm and control costs is minimized, may be either to the left or to the right of the optimal point L* in Figure 2.

If the incremental costs of reducing exposure are small enough, the optimal control level under the LNT model will be very stringent, with very low exposure (such as exposure level A in Figure 1). At these small exposure levels, reductions in exposure will reduce harm under the linear model but may have little effect or may even reduce beneficial effects under the hormetic model, and so the hormetic model would call for less stringent controls. For these high exposure levels, the benefit of incrementally reducing exposure is larger under the hormetic model than under the LNT model, and so more stringent controls would be justified.

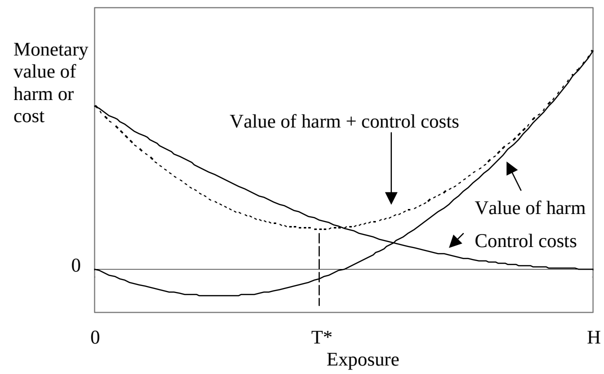

Figure 3 – Optimal regulation under the hormetic model

Optimal Regulation for a Population

The analysis in Figures 2 and 3 is appropriate for an individual. For a population, determining the optimal regulatory target can be more difficult under the hormetic model than under the LNT model. The difficulty arises because decisions that influence exposure levels in a population are likely to differentially affect individuals whose exposure levels and possibly exposure-response functions differ because of environmental, behavioral, genetic, or other factors. Under the LNT model, reducing exposure is always beneficial. In contrast, under the hormetic model, population-level decisions must balance the benefit of reducing exposure to individuals whose exposure to a substance is above the level at which they would receive the greatest health benefit (to the right of exposure level A in Figure 1), against harms to individuals whose exposure is less than the level that would best promote their health (to the left of exposure level A in Figure 1).

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FURTHER READING/REFERENCES:
Calabrese, Edward, "Hormesis: a revolution in toxicology, risk assessment and medicine" *EMBO Reports,* Special Issue Vol 5, Oct. 2004 pp. 37-40.

PEER REVIEWER:
George Gray, Ph.D.

Conclusion

Although the linear no-threshold model is often used when setting environmental regulatory standards, proponents of an alternative hypothesis, hormesis, suggest that the relationship between exposure and harm may be better represented as a J-shaped function for many environmental toxicants. Hormesis implies that the risk of harm at low exposure levels is smaller than implied by the linear no-threshold model (indeed, that low-level exposure produces beneficial rather than adverse effects), but it does not follow that dropping the standard LNT assumption in favor of the hormetic model implies that a substance should be regulated less stringently.

Whether hormesis implies a loosening or strengthening of regulations depends on the incremental cost of controlling exposure. If the additional cost of limiting exposure to very low levels is relatively small, then it is optimal to regulate a substance more stringently if its effects are characterized by the linear no-threshold model than by the hormetic model. This follows because at very low exposure levels, further reductions in exposure would reduce harms under the LNT model but the same exposure reductions would reduce beneficial effects under the hormetic model. In contrast, if the incremental cost of reducing exposure is relatively high, then only modest emission reductions are justified under the LNT model. For these exposure levels, the incremental benefit of reducing exposure under the hormetic model is larger than under the LNT model, and so hormesis will require more stringent regulations.

For additional discussion of the implications of hormesis for environmental-health regulation, see "Economic Implications of Hormesis," by James K. Hammitt, with commentaries by Charles Griffiths, Richard D. Morgenstern, Kerry Smith and Mary F. Evans, and Jonathan Weiner, and the response by Hammitt. These papers are published in the *BELLE Newsletter,* Volume 12, Number 1, March 2004, and in *Human and Experimental Toxicology,* Volume 23, Number 6, June 2004.