Legal criteria and judicial precedents relevant to incorporation of hormesis into regulatory decision-making

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Received 8 June 2001; accepted 20 November 2001

Abstract

Neither US regulatory programs nor the US legal system have yet to be confronted with a regulatory decision in which hormesis played a significant role. Nonetheless, with the growing scientific attention being paid to the large body of data suggesting that many otherwise toxic agents may exhibit a protective effect at low concentrations, it is highly likely that the regulatory and legal systems will soon face the challenge of whether and how hormesis should be incorporated into regulatory decisions. This article describes the legal criteria and judicial precedents that are likely to govern the incorporation of hormesis into regulatory decision-making. While these various legal requirements will be influential in agency decision-making with respect to hormesis, it is likely that, due to the fundamental shift in assumptions that hormesis represents, legal decision-makers will largely defer to scientific opinion, as expressed through the recommendations of agency scientific advisory boards and other scientific entities. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Hormesis; Legal requirements; Judicial decisions; Regulatory decision-making

1. Introduction

Hormesis is the protective or stimulatory effect at low doses of an agent that is otherwise toxic at higher doses. It is, therefore, characterized by a ‘U-shaped’ dose–response curve. Hormesis appears to result from an overcompensation to a disruption in homeostasis caused by an external agent (Calabrese and Baldwin, 2001).

The US Congress has never addressed the role that hormesis should play in regulatory decisions. No US regulatory agency has yet to base a regulatory action on hormesis, in whole or in part. No reported judicial decision in the United States has ever mentioned hormesis. To the author’s knowledge, other national, international and state entities have likewise failed to give legal significance to hormesis in regulatory decision-making. Given the silence to date of legislatures, regulatory agencies and courts on the subject of hormesis, one might conclude that there would be little to say about the legal implications of hormesis.

Hormesis has also long been marginalized in the scientific community, notwithstanding a large
body of supporting scientific data (Calabrese and Baldwin, 2000; Mossman, 2001). In recent years, however, there has been renewed scientific support for and interest in hormesis (Calabrese and Baldwin, 2001). With this renewed scientific interest, combined with the trend toward regulating ever-lower levels of toxic substances, it is likely, if not inevitable, that the legal system will soon confront hormesis in regulatory decision-making. This article draws on relevant legal precedents and analogies to examine the legal issues that are likely to be raised by regulatory consideration of hormesis.

The existence of hormesis might alter the optimal level of regulatory standards directed at low levels of toxic substances exhibiting a hormetic effect. For example, hormesis may justify setting a regulatory standard, such as an occupational exposure standard, at a higher level than might otherwise be feasible, because the lower standard would be in the hormetic region. Hormesis may also suggest applying smaller uncertainty factors used to calculate reference doses (RfDs) and reference concentrations (RfCs) representing the ‘safe’ level of non-carcinogens, because larger uncertainty factors would push the RfD or RfC into the dose range where hormesis occurs (Calabrese, 1996; Calabrese and Baldwin, 1998a). In a similar way, agencies have applied smaller uncertainty factors to essential nutrients such as selenium that are toxic at higher concentrations, to avoid setting the ‘safe’ level below the recommended intake level. Hormesis could also be used to set less stringent clean-up standards for hazardous waste sites, and perhaps even the existence of hormetic effects from low concentrations of some compounds in the waste mixture could be used to ‘set-off’ or ‘cancel out’ adverse effects from other compounds present in the same waste mixture (Juni and McElveen, 2000).

However, before hormesis is incorporated into regulatory decision-making, it would have to satisfy four criteria. First, there must be credible scientific evidence of hormesis for the specific agent or activity being regulated. Secondly, consideration of hormesis must alter the regulatory outcome, in that the adopted standard would be different if hormesis was considered than if it were ignored. Thirdly, the regulatory agency must have the statutory authority to consider hormesis under its pertinent regulatory statute(s). Finally, the agency must be receptive to considering evidence of hormesis. These four criteria for regulatory and legal acceptance of hormesis are discussed below, along with relevant precedents from analogous judicial decisions and regulatory actions.

2. Credible scientific evidence of hormesis

Hormesis is unlikely to have any relevance to regulatory decision-making unless it is supported by credible scientific evidence for the specific agent being regulated. Hormesis represents a fundamental departure from the current conventional wisdom and regulatory assumption that toxic substances exhibit a monotonic dose–response. Regulatory agencies will, therefore, most likely require conclusive scientific evidence of hormesis before accepting and applying this new concept.

A threshold question, though, is just how compelling the evidence for hormesis should be before it can be used to affect regulatory decisions? Traditional risk assessment policies and practices of US federal agencies involve the establishment of ‘conservative’ (i.e. err on side of protection) ‘default’ assumptions or options that can only be displaced in a specific risk assessment by compelling scientific data. For example, the National Research Council (NRC) of the US National Academy of Sciences observed that the default options are routinely applied by agencies such as the US Environmental Protection Agency (US EPA) in individual risk assessments ‘in the absence of convincing scientific knowledge’ (NRC, 1994).

Likewise, the National Toxicology Program (NTP), in its listing of criteria for the Biennial Report on Carcinogens, requires ‘compelling data’ that otherwise applicable animal studies for the agent in question are not relevant for humans before the agency will depart from its default assumption that animal studies are relevant predictors of human carcinogenicity (NTP, 2000, p. 1–2). As a final example, the US EPA’s recently proposed revisions to its carcinogen risk assessment guidelines, which are widely perceived as providing for greater flexibility in departing from default assumptions based on scientific data, nev-
ertheless state that ‘if the default concerns an inherently complex biological question, large amounts of work will be required to replace the default’ (US EPA, 1996, p. 17966).

The implicit default assumption in current risk assessment procedures, especially for carcinogenic substances, is that the dose–response function conforms to a linear, non-threshold (LNT) model. Departing from that default assumption by accepting the existence of hormesis would, therefore, appear to require ‘convincing’ or ‘compelling’ scientific evidence. This high evidentiary threshold for consideration of hormesis appears to be the position of some regulators. For example, in an April 24, 1998 speech, Commissioner Greta Joy Dicus of the Nuclear Regulatory Commission stated that evidence for hormesis ‘must become overwhelming and be demonstrated in humans before there will be serious consideration to moving away from the LNT assumptions that underlie the present radiation protection framework’ (emphasis added).

The current practice of requiring compelling evidence before departing from risk assessment default options has been criticized as unduly inflexible (McClellan and North, 1994). However, even putting aside such objections, it is not clear that the historical practice of requiring compelling data before departing from a default should apply to hormesis. The policy rationale given for requiring compelling evidence for departure from a conservative default is that we prefer to err on the side of over-protecting human life vs. preventing excessive economic expenditures (Finkel, 1994). Because conservative default assumptions tend to err on the side of protecting human life vs. preventing excessive economic expenditures, any policy tilt should be toward recognizing real hormetic effects, at least when they are comparable in magnitude to the estimated health benefits from reducing toxic exposures over the same dose range if hormesis did not exist. To the extent this approach is credited, hormesis should be considered in regulatory decisions, at a minimum, whenever the balance of scientific evidence suggests that such effects may be real, without requiring the higher standard of ‘compelling’ or ‘convincing’ evidence needed for departure from most other risk assessment defaults.

As a practical matter, it is nevertheless unlikely that a regulatory agency will seriously consider hormesis in the absence of strong scientific support. Hormesis represents a dramatic departure from the traditional LNT model and the regulatory goal of reducing exposures to toxic agents as low as possible. It will also impose additional resource burdens on agencies to consider the relevant data and respond to public comments on the issue. Agencies are, therefore, unlikely to be the first to take hormesis into account in making a regulatory decision unless the argument for hormesis is accompanied by substantial scientific support. There does appear to be both a substantial theoretical foundation and sufficient database of experimental results to support the existence of hormesis as a general phenomenon (Calabrese and Baldwin, 1999b; Calabrese et al., 1999). To be applicable to a specific regulatory proceeding, however, there

unnecessary regulatory expenditures and provide additional health benefits. Thus, the balance of consequences is not dollars vs. lives as for most default assumptions. Rather, failing to recognize hormesis when it exists (i.e. incorrectly adhering to LNT default) could cost both lives and dollars, whereas precipitously recognizing hormesis, where it is not a significant factor (i.e. prematurely departing from default), would cost lives only. Therefore, it does not follow that the preference for lives over dollars should necessarily weigh against considering hormesis (Cross, 2000).
will need to be convincing data for the particular agent being regulated.

In addition to requiring compelling data on the existence of a hormetic response for the regulated agent, a regulatory agency may also require adequate understanding of the mechanism underlying hormesis to have sufficient confidence to base a regulatory decision on hormesis. Regulatory agencies do not always require understanding of the mechanism of toxicity before taking regulatory action. For example, in adopting new national ambient air quality standards for fine particulate matter in 1997, US EPA noted that the absence of a demonstrated mechanism of toxicity ‘is an important caution,’ but ‘the absence of evidence of a particular mechanism is hardly proof that there are no mechanisms that could explain the effects observed so consistently in the epidemiological studies.’ (US EPA, 1997, pp. 38657–38658). This precedent could be used to argue that if a hormetic effect is consistently observed in credible scientific studies, the absence of a demonstrated mechanism for hormesis should not prevent it from being considered in regulatory decisions.

On the other hand, there is also a set of regulatory precedents in which an agency has been reluctant to depart from a risk assessment default principle unless and until the mechanism for the alternative assumption has been elucidated. The US EPA’s 1996 proposed revised carcinogen risk assessment guidelines require an understanding of the agent’s mode of action, including an understanding of the critical events leading to neoplasia, before departing from default principles used to assess carcinogenic risk (US EPA, 1996; Dellarco and Wiltse, 1998). A specific example of this requirement for mechanistic understanding is the US EPA’s decision to exclude from a weight-of-the-evidence evaluation of carcinogenic hazard data on kidney tumors in male rats that are shown to be caused by a rodent-specific mechanism involving the accumulation of alpha2u-globulin protein (US EPA, 1991). These precedents suggest that a regulatory agency such as the US EPA may be reluctant to depart from the linear, non-threshold default assumption in the absence of a mechanistic understanding of hormesis.

While no agency has yet to base its regulatory decision on hormesis, the US EPA recently became the first agency to directly address, and reject, hormesis in a regulatory decision. In December 2000, the US EPA finalized its drinking water standards for radionuclides under the Safe Drinking Water Act. The US EPA set a maximum contaminant level goal (MCLG) for radionuclides of zero based on the LNT model, and maximum contaminant levels (MCLs) for various radionuclides at the lowest feasible level above the zero MCLG. One public commentator argued that the US EPA should have set a less stringent standard based on hormesis and adaptive response. This argument was squarely, but summarily, addressed and rejected by the US EPA:

‘The agency finds that, based on available scientific evidence, these phenomena (hormesis, adaptive response) are not relevant to environmental radiation protection. Neither has been shown to occur at environmental dose levels. Neither has been shown to influence the dose response for induction of radiation induced cancer. Hormesis has not been demonstrated in normal healthy active populations of mammals, much less in humans… Recent usage of the term ‘Radiation Hormesis’ implies the discussion relates to beneficial effects. It should not, however, imply absence of radiation carcinogenesis’” (US EPA, 2000, p. 76722).

As will be discussed below, this summary rejection of hormesis without careful consideration of the merits, and explanation of the reasons for rejecting the submitted evidence, is legally risky for an agency such as the US EPA. Nevertheless, this first example of a regulatory agency considering hormesis indicates that agencies will be skeptical of such evidence, and will require strong scientific support before taking hormesis arguments seriously. The availability of adequate scientific support will be a challenge, given that hormesis occurs at low doses, where toxicological data are most limited and uncertain (Mossman, 2001).

3. Hormesis must be relevant to the regulatory outcome

A second criteria for regulatory consideration of hormesis is that the consideration of the hormetic
effect must change, or at least have a substantial potential to change, the regulatory outcome. No agency is likely to assume the resource and political costs of accepting hormesis if it makes no difference to the regulatory outcome. For hormesis to be relevant, the agency must, for example, be considering promulgating a standard in the range of exposure levels in which hormesis occurs and exposure may be beneficial. Although there are a few exceptions with larger effects, in most cases, hormetic responses have a modest magnitude and range, typically with a maximum protective effect 30%–60% greater than the background level in unexposed controls, and expressed over a dose range spanning, at most, a factor of 10–20 (Calabrese et al., 1999). When a regulatory agency is considering setting a standard in this range, the evidence for hormesis may suggest setting a higher standard, above the level at which the exposure begins providing a net protective effect.

Of course, for hormesis to be applied in such a manner, it is necessary to have a reasonably precise approximation of the ‘tipping point’ (Cross, 2000) at which exposures shift from being harmful to protective. Significant uncertainties are inevitable in any attempt to apply hormesis. Not only will the tipping point where the exposure shifts from detrimental to beneficial be uncertain, but so too will be the magnitude of the hormetic effect at any particular exposure level below the tipping point.

Other major uncertainties may likewise diminish the utility, and thus, the relevance of hormesis. One area of uncertainty will be the consequences of cumulative exposures on the hormetic response, both with respect to other exposures to the same agent, and exposures to other toxic substances, to the extent that hormesis is a cumulative exposure rather than agent-specific response (Lave, 2001). In other words, it may be that an individual’s exposure to the same or other toxic substances will affect the probability of observing hormesis at a particular exposure level for the regulated agent. If this is the case, it may be necessary to discern other exposures to the individual in judging the relevance and occurrence of hormesis, which could make problematic the application of hormesis to a population group (which is usually the relevant focus in setting a regulatory standard).

Similar concerns are likely to be raised by the existence of susceptible sub-groups, which may experience hormesis at a different exposure level than the general population, or not at all (Lave, 2001). Again, the application of a population-based hormesis factor may be objectionable. It may also be the case that the same toxic agent induces different toxic endpoints, but with different hormesis profiles. For example, a chemical might cause both cancer and non-neoplastic systemic disease, which have non-overlapping hormetic ranges of exposure. In the past, it was typical to focus primarily on the health effect with the lowest adverse effect level in setting regulatory standards, given that a ‘safe’ level for that effect would also be likely to protect against other adverse effects that occur at higher exposure levels. If different adverse effects have different exposure levels at which they exhibit hormesis, it may no longer be preferable to focus solely on the lowest adverse effect in making regulatory decisions.

These uncertainties in applying hormesis are both inevitable and foreboding. Yet, do these uncertainties necessarily have greater force for hormesis than for other low-dose models? Under the current regulatory approach, including decisions based on the LNT model, uncertainties related to these same factors — such as cumulative exposures, susceptible sub-groups, and different health endpoints — are, mostly out of necessity, largely ignored or at least under-emphasized. To be sure, there is a growing emphasis in developing new risk assessment approaches to address such factors. However, given that these uncertainties and complications apply to risk assessment across the board, they should not automatically single out hormesis for disqualification (see Teeguarden et al., 2000). On the contrary, as with other low-dose models, risk assessors and managers should simply apply the best available understanding and data in addressing such uncertainties.

4. The agency must have statutory authority to consider hormesis

A prerequisite to regulatory consideration of hormesis is that such consideration is permissible
under the agency’s relevant regulatory statute. Statutory provisions for setting environmental standards can be grouped into three major categories. Technology-based statutory provisions require environmental standards to be based on the ‘best available’ technology or some similar formulation based on technology. For example, the Clean Air Act requires emission standards for hazardous air pollutants to be based on the maximum available control technology or ‘MACT.’ Because such statutes generally do not provide for consideration of risk, they would leave no opportunity for consideration of hormesis.

A second category of statutes includes those that permit consideration only of risk, and require the agency to set standards at an acceptable risk level. For example, the Clean Air Act requires the US EPA to set national ambient air quality standards (NAAQS) at a level ‘requisite to protect the public health’ with ‘an adequate margin of safety.’ The US Supreme Court has recently affirmed that this statutory language requires the agency to set standards based only on scientific evidence of risk, without taking into account economic costs or technological feasibility (Whitman vs. ATA, 2001). For these and other risk-based standards, hormesis would seem to be directly relevant, in that the agency would not want to set an acceptable risk standard below the tipping pint at which hormesis occurs, where the marginal effect of the standard on public health would be detrimental.

One complication for applying hormesis under such ‘acceptable risk’ statutes is that the risk-based standard-setting often focuses on the most sensitive sub-populations. An agency could consider the level of hormesis in these vulnerable groups only, but the problem then presented is that the standard promulgated to protect the sensitive sub-population (including consideration of hormesis for such individuals) may be set at a stringent level within the hormetic range for the general population (Gaylor, 1998). Thus, the existence of hormesis creates a potential new trade-off between the health of ‘normal’ people vs. susceptible sub-groups. In the absence of hormesis, setting standards at a more stringent level to protect sensitive sub-populations did not jeopardize the health of the general population (indeed, it may have provided an additional margin of safety), but only imposed additional costs of compliance. If setting more stringent standards to protect susceptible sub-groups will now increase the risks to other people because of hormesis, difficult policy and ethical problems will be presented that are beyond the scope of this paper.

The third major category of statutes includes those that require standards to be based on balancing of costs and benefits. An example is the Toxic Substances Control Act, which limits the US EPA to regulating ‘unreasonable’ risks, to be determined by a cost–benefit analysis of reducing risk. Hormesis would again appear to fit into this decision-making approach. Cost–benefit analysis would weigh against regulating in the hormetic range, since such regulation would produce negative health benefits at the margin while producing positive cost impacts, thus failing a cost–benefit test. At exposures above the hormetic range, however, hormesis may weigh in favor of more stringent standards (Cross, 2000). This is because the existence of hormesis at low exposure levels necessarily means that the dose–response curve above such levels slopes more steeply towards zero risk, and thus any incremental reduction in exposure in this range would produce a higher benefits estimate due to the steeper dose–response curve.

Hormesis would, therefore, appear to ‘fit’ regulatory decision-making under both acceptable risk and cost–benefit balancing statutes. There is no role for consideration of hormesis under technology-based statutes, which has led at least one commentator to suggest that technology-based statutes should be disfavored because of the potential to produce irrational results when hormesis is disregarded (Cross, 2000). The next question is whether the consideration of hormesis is permissible under such statutes, because even if a factor such as hormesis is potentially relevant to regulatory decision-making, it nevertheless cannot be considered if Congress intended to exclude it from consideration.

No US environmental statute or its legislative history specifically mentions the term ‘hormesis’ or otherwise appears to address this concept. This Congressional silence could mean that hormesis is not expressly precluded and can be considered, or
alternatively, that it is not permissible to consider hormesis because it has not been specifically authorized by Congress. Courts have been somewhat inconsistent in construing an agency's authority to consider a factor for which Congress has been silent. The general rule on interpreting ambiguous statutory language, however, is the so-called Chevron standard which holds that courts will defer to an agency's 'reasonable' interpretation of an ambiguous statute (Chevron USA vs. NRDC, 1984). Under this standard, an agency's decision to consider or not consider hormesis would, therefore, appear to be entitled to some deference.

The most relevant precedent suggesting that an agency may be restricted from considering hormesis, notwithstanding Chevron deference, is a judicial decision over-turning the occupational exposure standard for formaldehyde promulgated by the Occupational Safety and Health Administration (OSHA) (Int. Union, UAW vs. Pendergrass, 1989). The court held that OSHA had improperly used the maximum likelihood estimate (MLE) rather than the upper confidence limit (UCL) to calculate the risks of occupational exposure to formaldehyde. The court found that the UCL but not the MLE model was consistent with a linear dose–response assumption, and that OSHA provided no rationale for departing from its traditional linear, no-threshold dose–response assumption. This decision stands for the proposition that an agency cannot depart from its established practice without an adequate explanation, rather than that a non-linear, no-threshold model is per se unlawful. As another decision by the same court explained, ‘an agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored,... and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute’ (Greater Boston Television Corp. vs. FCC, 1971). Thus, if an agency departs from its traditional linear, no-threshold assumption to consider hormesis, it would need to explain why this new approach is justified by new scientific understanding and evidence for hormesis.

The US EPA's recently proposed revisions to its carcinogen risk assessment guidelines may pave the way for greater flexibility to incorporate hormesis into regulatory decision-making, and to justify a departure from the linear, no-threshold assumption of the past (US EPA, 1996). These new guidelines give a greater emphasis to mode-of-action and mechanistic data in evaluating dose–response relationships, with less weight given to default assumptions. These guidelines should encourage improved empirical investigation of the dose–response curve in the low-dose region, which should both improve the likelihood of discovering and characterizing hormetic responses for specific agents, and justifying departures from default assumptions to apply this information in risk assessment (Teeuwarden et al., 2000). The US EPA’s neurotoxicity risk assessment guidelines promulgated in 1998 appear to go even further and expressly recognize that ‘dose–response curves may exhibit not only monotonic but also U-shaped or inverted U-shaped function’ that may reflect the ‘activation of compensatory or protective mechanisms’ (US EPA, 1998, p. 26945).

There are some additional legal arguments and precedents suggesting that when hormesis is raised with adequate scientific support, a regulatory agency not only may, but indeed must, give appropriate consideration to hormesis in making its regulatory decision. Many environmental statutory provisions require the agency to protect ‘the public health,’ or ensure against ‘unreasonable’ or ‘significant’ risk. Since hormesis is directly pertinent to a determination of public health or unreasonable risk, failure to consider hormesis would seem to be arbitrary and capricious. The most relevant legal precedent for this proposition, and in support of consideration of hormesis generally, is the US Court of Appeals for the D.C. Circuit’s 1999 decision in American Trucking Associations vs. EPA, which invalidated US EPA’s national ambient air quality standards (NAAQS) for ozone and particulate matter (ATA vs. EPA, 1999). This case did not address hormesis, but in a closely analogous analysis, held that US EPA acted arbitrarily in failing to consider the health benefits in addition to the adverse health effects of ground-level ozone.

Ozone is known to cause adverse respiratory effects, but like stratospheric ozone, it also provides certain health benefits by absorbing harmful
UV-B radiation. The Department of Energy, in testimony to US EPA’s Clean Air Scientific Advisory Committee on US EPA’s proposed ozone standard, stated:

“[i]t is known that UV-B penetration in the atmosphere, and its associated health risks, are affected by total column ozone, and that any decrease in atmospheric ozone will result in increased penetration of UV-B to the earth’s surface. Therefore, tropospheric ozone pollution helps to attenuate UV-B-related health effects at the same time that this ozone is causing other health effects. When developing new ozone standards, we think that it is important to use all the available scientific information to assure that a balanced position addresses this conundrum”.

Using values from US EPA’s own stratospheric ozone risk assessment, the Department of Energy estimated that a 0.5% decrease in total column ozone as a result of US EPA’s proposed more stringent ground level ozone standard would result in: (i) 2000–11000 extra cases of non-melanoma skin cancer per year; (ii) 130–260 extra cases of melanoma, including 25–50 deaths per year; and (iii) 28000 new cataract cases per year.

In justifying its ozone standard, the US EPA claimed only that its standard would reduce morbidity ranging from mild and reversible lung irritation to more serious chronic lung disease, but would not result in any additional lives saved. Given the DOE estimate that the ozone standard would result in an additional 25–50 deaths per year from UV-B induced melanoma, the net effect of the ozone standard on mortality would be to increase deaths, which would be accompanied by both increases and decreases in various types of non-fatal health effects. A published analysis by two Office of Management and Budget analysts produced similar estimates, and concluded that the monetized value of the ‘the UV-B-related adverse health effects of reducing tropospheric O₃ to comply with the current O₃ NAAQS or to attain US EPA’s proposed more stringent NAAQS may be similar in magnitude to the respiratory-related beneficial health effects of such an O₃ reduction’ (Lutter and Wolz, 1997).

This case, therefore, closely resembled the issues that would be presented if an agency was asked to consider the health benefits from hormesis in setting a health-based regulatory standard. The US EPA was faced with evidence that a substance with known hazardous properties at some concentrations also had beneficial health impacts (in this case, at the same exposure levels, whereas with hormesis the harmful and beneficial effects occur at different exposure levels). Rather than considering both the harmful and beneficial health effects of ground-level ozone, the US EPA chose to base its standard only on consideration of the adverse effects of ground-level ozone. The US EPA’s primary argument for excluding consideration of the health benefits of ozone was a legal argument that the statute precluded such consideration. The relevant provision of the Clean Air Act directs that the US EPA is to consider ‘all identifiable effects on public health’ of the pollutant (ozone) ‘in the ambient air’ (Clean Air Act, § 109(b), 1990). The US EPA concluded argued that ‘all identifiable effects on public health’ only included ‘adverse’ effects and not the health benefits of ozone from blocking UV-B.

The US EPA’s decision to exclude the health benefits of ground-level ozone, as well as other aspects of its overall regulatory decision, were then challenged in court. The US Court of Appeals for the D.C. Circuit squarely rejected the US EPA’s argument that it need not consider the health benefits of ozone (ATA vs. EPA, 1999). The court concluded that the statute is unambiguous — when it directs the US EPA to consider ‘all identifiable effects on public health,’ the statute means ‘all’ effects and not just ‘adverse’ effects as US EPA had argued. Moreover, even if the statute were ambiguous, the court continued that ‘it seems bizarre that a statute intended to improve human health would, as US EPA claimed at argument, lock the agency into looking at only one half of a substance’s health effects in determining the maximum level for that substance’ (ibid. at 1052).

While the US EPA successfully appealed other parts of the court’s decision to the Supreme Court, it did not appeal the section of the court’s decision requiring consideration of the health benefits of ozone, at least in part because not a single judge on the D.C. Circuit (either in the initial three-judge decision or in a subsequent en banc appeal to the entire court) expressed any support for the
US EPA’s position on this issue. This decision thus creates a powerful precedent that a regulatory agency directed to protect the public health not only may, but in fact must, consider both the adverse and beneficial health effects of a hazardous substance. This holding would seem to both permit and require an agency to consider scientifically-credible evidence of hormesis in setting environmental standards, even if the regulatory statute under which the agency is acting is ambiguous on the issue of hormesis (see also Juni and McElveen, 2000).

5. Agency willingness to consider hormesis

Even if an agency has the statutory authority to consider hormesis, it is unlikely that an agency will incorporate hormesis into its regulatory decisions unless it affirmatively believes in the scientific merits and regulatory importance of hormesis, or is ordered by a court to give greater consideration to hormesis. A recalcitrant agency that is skeptical of hormesis will likely have much greater flexibility, regardless of its statutory mandate, to downplay or even disregard credible scientific evidence for hormesis.

There are a number of reasons why a regulatory agency may be reluctant to embrace hormesis. Hormesis will involve substantial uncertainty, which will only increase the complexity and divisiveness of the agency’s regulatory activities. Hormesis will also impose additional resource demands on regulatory agencies, both with respect to obtaining adequate data to characterize the hormetic response at low doses, and then reviewing and applying that data in the regulatory decision. Regulatory risk assessment is already a very complicated and resource-intensive undertaking, and regulators are likely to resist adding another layer of complexity and potential controversy by incorporating hormesis. Hormesis is also likely to be controversial with the public, as the assertion that some of the most toxic pollutants known may be beneficial at low concentrations is likely to be met with incredulity and ridicule by many in the general public and media. The concept of hormesis is likewise contrary to the traditional institutional mission of regulatory agencies to reduce toxic exposures as low as possible, which is likely to generate internal agency opposition to giving much weight to hormesis.

Given these factors, it will not be surprising if agencies resist incorporating hormesis into regulatory decision-making, and there is already some evidence of such resistance. For example, as discussed above, the US EPA summarily rejected as irrelevant evidence of hormesis in its December 2000 rulemaking on drinking water standards for radionuclides. Such a cursory rejection of hormesis is legally risky for agencies, however. There is a well-established principle of administrative law that an agency cannot simply ignore a potentially relevant factor in making and defending its regulatory decision. For example, the US Supreme Court has held that an agency must ‘examine the relevant data and articulate a satisfactory explanation for its action’ (Motor Vehicle Manufacturers Ass’n vs. State Farm, 1983, p.31). Thus, an agency that fails to carefully consider and explain its rationale for rejecting evidence (i.e. of hormesis) submitted to the agency would be in violation of its duty to give ‘reasoned consideration to all the material facts and issues’ (Greater Boston Television Corp. vs. FCC, 1971, p. 851). While courts usually defer to an agency’s expertise, offhand rejection of evidence is not entitled to deference because in the absence of a careful review of the evidence, the agency ‘simply has not exercised its expertise’ (Public Citizen vs. Tyson, 1986, p. 1505).

There are a number of relevant judicial analogies where a court has over-turned a regulatory agency’s perfunctory dismissal of evidence of countervailing risks when promulgating environmental, health or safety standards. In the Clean Air Act ozone standard case described above, in which the US EPA refused to consider the health benefits of ozone, the agency supplemented its statutory argument that it was not permitted to consider such benefits with a secondary argument that, even if it were authorized, the alleged benefits of ozone were inflated and moreover were too uncertain and trivial to warrant serious consideration. The court rejected this US EPA argument as well. The court first held that it need not address the US EPA’s argument that petitioners had inflated the results
of studies on the health benefits of ozone because ‘the EPA chose to give the studies no weight at all.’ As to the US EPA’s argument that health benefits were too uncertain to quantify, the court held that ‘we can see no reason for imposing a higher information threshold for beneficial effects than for maleficent ones…’ (ATA vs. EPA, 1999, p. 1053).

In another case, the National Highway Transportation Safety Administration failed to give sufficient consideration to the detrimental safety consequences that may result from its corporate average fuel economy (CAFE) standards for motor vehicles, which resulted in increased numbers of smaller, less crashworthy vehicles. In a strongly worded opinion, the reviewing court rejected the agency’s decision because it failed to seriously consider these safety trade-offs:

“In deciding whether to relax the… CAFE standard for model year 1990… NHTSA confronted a record suggesting that the refusal to do so would exact some penalty in auto safety. Rather than affirmatively choosing extra energy savings over extra safety, however, NHTSA obscured the safety problem, and thus its need to choose… The requirement of reasoned decisionmaking... prevents officials from covering behind bureaucratic mumbo-jumbo” (Competitive Enterprise Inst. vs. NHTSA, 1992, pp. 322, 327).

Similarly, another court rejected US EPA’s proposed ban on asbestos products because the agency had failed to take seriously the health trade-offs from substitute products for asbestos:

“EPA cannot say with any assurance that its regulation will increase workplace safety when it refuses to evaluate the harm that will result from the increased use of substitute products....Eager to douse the dangers of asbestos, the agency inadvertently actually may increase the risk of injury Americans face. The EPA’s explicit failure to consider the toxicity of likely substitutes thus deprives its order of a reasonable basis” (Corrosion Proof Fittings vs. EPA, 1991, p. 1221).

These cases establish that an agency is likely to be overturned by the courts when it conducts only a superficial analysis of countervailing risks. A similar judicial response is likely if an agency summarily rejects credible scientific evidence of hormesis, which like the countervailing risk cases involves potential health disbenefits from overly stringent regulation.

On the other hand, if an agency considers seriously the scientific evidence for hormesis, but ultimately rejects that evidence based on the scientific merits and adequately explains its decision, the agency is likely to receive considerable deference from a reviewing court. As the Supreme Court has directed, ‘[w]hen examining this kind of scientific determination, as opposed to simple findings of fact, a reviewing court must generally be at its most deferential’ (Baltimore Gas & Elec. Co. vs. NRDC, 1983, p. 103). Judges usually (although not always) recognize their own limited authority and expertise to second-guess agency scientific determinations — as stated in one judicial opinion, ‘substantive review of mathematical and scientific evidence by technically illiterate judges is dangerously unreliable’ (Ethyl Corp. vs. EPA, 1976, p. 67).

Nonetheless, judicial deference to agency scientific determinations is not absolute, particularly where it appears that the agency is relying on out-of-date or unsupported scientific assertions. For example, one court held that regulation ‘must remain attuned to our rapidly expanding knowledge and technology’ (Environmental Defense Fund vs. Costle, 1978, p. 344). Another judicial decision stated that a regulation intended to protect public health must ‘accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health’ (Lead Indus. Ass’n vs. EPA, 1980, p. 1157). An agency decision that fails to incorporate up-to-date and credible scientific evidence thus risks being overturned on the ground that the ‘agency acted arbitrarily in failing to utilize the best scientific evidence available’ (American Tun-aboa Ass’n vs. Baldridge, 1984, p. 1017).

Judicial scrutiny of an agency’s scientific findings is likely to be most rigorous under statutes that expressly require the agency to use the ‘best’ available science. For example, the Safe Drinking Water Act as amended in 1996 requires the US EPA to use ‘the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practic-
es’ (Safe Drinking Water Act, § 300g-1(b)(3)(A), 1996).

A court is likely to be least deferential to an agency’s scientific findings when the conclusion of the agency are at odds with the recommendations of its own scientific advisors. In International Harvester Co. vs. Ruckelshaus (1973), the D.C. Circuit held that a heightened standard of explanation was required by the agency to over-ride the advice of scientific advisors to the agency. More recently, that same court over-turned the US EPA’s continued reliance on the no-threshold assumption to set drinking water standards for chloroform because such an assumption was contrary to the best available evidence, defined in part by the conclusions of two scientific advisory committees commissioned by US EPA who supported a non-linear dose–response relationship (Chlorine Chemistry Council vs. EPA, 2000). This decision concerned a regulation under the Safe Drinking Water Act, which, as described above, expressly requires regulatory decisions to be based on the best available scientific evidence.

There is already some evidence that the science advisory boards of agencies such as the US EPA are beginning to address hormesis. For example, a 1999 report by the US EPA’s Scientific Advisory Board (SAB) criticized a draft White Paper assessing risks from indoor radon because it ‘ignores the possibility that at low levels, radiation may stimulate the immune system (hormesis)’ (SAB, 1999, p. 10). The SAB report continued that ‘[a]lthough the Committee is not advocating the hormetic hypothesis or other threshold or non-linear exposure–response relationships, from the evidence now available, a threshold exposure (i.e. a level of exposure below which radon has no effect) cannot be excluded’.

Similarly, at its 23 January, 2001 meeting, the SAB Dioxin Reassessment Review Subcommittee discussed the application of hormesis to the agency’s pending risk assessment for dioxin. The minutes of that meeting state that ‘the Committee felt the need to address [hormesis] without making a judgment on its existence,’ but that the committee would instead use the term ‘non-monotonic dose response,’ thereby ‘avoiding the use of the word ‘hormesis,’ but not the underlying concept.’ These examples demonstrate that the potential scientific and regulatory significance of hormesis is percolating up to the agency’s science advisors, who recognize the potential (albeit uncertain) scientific and regulatory significance of the concept, as well as its controversial political nature.

In sum, an agency predisposed against considering hormesis can probably withstand judicial challenge if it rejects such evidence after careful scientific scrutiny and thorough explanation of the scientific basis for its determination. If the agency summarily rejects hormesis, or provides only a superficial explanation for its rejection, it will be vulnerable to judicial reversal. An agency will also be at heightened risk of being over-turned for rejecting hormesis out-of-hand if it regulates under a statute requiring regulations to be based on the best scientific evidence, and/or its own scientific advisory bodies have recommended giving greater weight to hormesis in the regulatory decision.

6. Conclusion

Hormesis has the potential to fundamentally change regulatory decision-making. Instead of trying to eliminate or at least minimize exposure to toxic substances, the focus of regulatory action could shift to optimizing exposures to toxic agents if hormesis is indeed generalizable, as a growing body of scientific evidence suggests (Calabrese and Baldwin, 2001). Hormesis will, therefore, present a significant challenge and potential paradigm-shift for regulatory and legal decision-makers.

The legal and regulatory systems have their own rules and policies that sometimes differ from those of science. In the case of hormesis, however, scientific consensus is particularly likely to lead the regulatory and legal conclusions, because this radical scientific concept has the potential to profoundly change regulatory assumptions and practices at low dose levels. Given its potential importance to regulatory outcomes, courts are unlikely to allow agencies to dismiss evidence of hormesis lightly when it is supported by solid scientific credentials, such as endorsement by the agency’s own scientific advisory committee. In the absence of such advisory committee endorsement,
legal decision-makers are unlikely to second-guess an expert agency’s reluctance to incorporate hormesis unless and until compelling scientific evidence for hormesis is marshaled and presented in a specific and relevant regulatory context. A court will be cautious about imposing such a significant scientific change-of-position on an expert agency without convincing scientific support. Therefore, in this context at least, it seems that science will lead and the law is likely to follow.

References

American Tunaboat Ass’n vs. Baldridge, 738 F.2d 1013 (9th Cir. 1984).
Calabrese EJ. Expanding the reference dose concept to incorporate and optimize beneficial effects while preventing toxic responses from nonessential toxicants. Regul Toxicol Pharmacol 1996;24:S68–S75.
Chlorine Chemistry Council vs. EPA, 206 F.3d 1286 (D.C. Cir. 2000)
Clean Air Act, § 109(b), 42 USC. § 7409(b) (as amended, 1990).
Corrosion Proof Fittings vs. EPA, 947 F.2d at 1221 (5th Cir., 1991).
Public Citizen Health Research Group vs. Tyson, 796 F.2d 1479 (D.C. Cir. 1986).
US Environmental Protection Agency and Risk Assessment


