BELLE NEWSLETTER

Biological Effects of Low Level Exposures

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PRECAUTIONARY PRINCIPLE AND HORMESIS

INTRODUCTION

This issue of the BELLE Newsletter addresses the issue of the Precautionary Principle and how it may be affected by the concept of hormesis. While the Precautionary Principle has been the object of much discussion and debate over the past few years the published works on the topic this will be the first attempt to explicitly address how hormesis, if accepted by the toxicology, risk assessment and regulatory communities, could affect national and international debate on the Precautionary Principle. This issue of the Newsletter contains two articles on this topic, by Cass Sustein and Paolo Ricci and their respective colleagues. Please note that the two papers were independently developed without information being shared during the writing of the manuscripts. As with other Newsletters I encourage comments to be sent to the BELLE office about this issue. Selected responses may be published in a forthcoming issue.

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HORMESIS, THE PRECAUTIONARY PRINCIPLE, AND LEGAL REGULATION

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1. Introduction

Many nations have shown mounting interest in a simple idea for the regulation of risk: In case of doubt, follow the precautionary principle.[1] Avoid steps that will create a risk of harm. Until safety is established, be cautious; do not require unambiguous evidence. In a catchphrase: Better safe than sorry.

The precautionary principle has been exceptionally influential in Europe. But it also helps to animate the American approach to environmental protection in general and to the regulation of toxic substances in particular. Most important, the Environmental Protection Agency uses a particular dose-response model to extrapolate risk of carcinogenic substances.[2] This model is expressly intended to be precautionary – to give the benefit of the doubt to safety. The EPA currently uses a linear non-threshold model, which assumes that the substance demonstrates no safe level of exposure.[3] Thus, for physical and chemical exposure to carcinogenic substances, the EPA assumes that all exposures, even those in extremely low doses, carry an associated cancer risk. This assumption drives a great deal of federal regulation, and it has not been successfully challenged in court.

Is the linear-threshold model correct? Is it even precautionary? An increasing body of evidence suggests that many toxic agents that are harmful at high levels are actually beneficial at low levels.[4] "Hormesis" is a mechanism that compels a different depiction of the dose-response relationship, one in which low levels of exposure produce benefits rather than harm.[5] For federal regulation, the problem is that when hormesis is involved, the use of a linear dose-response curve without safe thresholds will actually cause mortality and morbidity effects. Which default approach to the dose-response curve is precautionary[6]?

Our goal here is to explore this question. We do so both because of its intrinsic importance and because of its more general implications for the precautionary principle and regulatory policy. For toxic substances in particular, the possibility of hormesis demonstrates that the linear dose-response assumption cannot always be justified as "precautionary." The larger implication is that the precautionary principle has a quite general problem. Often risks exist on all sides of social situations. It is possible to take precautions against particular risks; but it is not possible to be globally precautionary. For toxic substances in general, no default rule can be justified on the ground that it "errs on the side of safety." With respect to regulation as a whole, it is often hopeless to advise people to give safety the benefit of the doubt. A more refined and sensible version of the precautionary principle amounts to balancing risks against risks, rather than accepting a general (and almost comically unhelpful) plea for risk aversion.

II. The Precautionary Principle and Its Limitations

A. Definitions

The precautionary principle has come to enjoy widespread international support.[7] But what does the principle mean or require? There are many definitions, and they are not compatible with one another.[8] We can imagine a continuum of understandings rather than a sharp dichotomy. The most cautious and weak versions suggest, quite sensibly, that a lack of decisive evidence of harm should not be a ground for refusing to regulate. The Ministerial Declaration of the Second International Conference on the Protection of the North Sea, held in London in 1987, proclaims: "Accepting that in order to protect the North Sea from possibly damaging effects of the most dangerous substances, a precautionary principle is necessary which may require action to control inputs of such substances even before a causal link has been established by absolutely clear scientific evidence."[9] The 1992 Rio Declaration states, "Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."[10] Similarly, the United Nations Framework Convention on Climate Change also offers cautious language: "Where there are threats of serious or irreversible damage, lack of full scientific certainty should not be used as a reason for postponing [regulatory] measures, taking into account that policies and measures to deal with climate change should be cost-effective so as to ensure global benefits at the lowest possible cost."[11]

The Wingspread Declaration, a highly influential statement of the precautionary principle, goes somewhat further: "When an activity raises threats of harm to

human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof."[12] The first sentence just quoted is a mildly more aggressive version of the statement from the Rio Declaration. It is more aggressive because it is not limited to threats of serious or irreversible damage. But in reversing the burden of proof, the second sentence goes further still, in a way that might well have implications for the control of toxic substances.[13] Of course everything depends on what those with the burden of proof must show in particular.

In Europe, the precautionary principle is understood in a still stronger way, suggesting that it is important to build "a margin of safety into all decision making."[14] According to one definition, the precautionary principle means "that action should be taken to correct a problem as soon as there is evidence that harm may occur, not after the harm has already occurred."[15] In a comparably strong version, it is said that "the precautionary principle mandates that when there is a risk of significant health or environmental damage to others or to future generations, and when there is scientific uncertainty as to the nature of that damage or the likelihood of the risk, then decisions should be made so as to prevent such activities from being conducted unless and until scientific evidence shows that the damage will not occur."[16] The Cartagena Protocol on Biosafety to the Convention on Biological Diversity, adopted in 2000, appears to adopt a strong version as well.[17] The Final Declaration of the First European "Seas At Risk" conference says that if "the 'worst case scenario' for a certain activity is serious enough then even a small amount of doubt as to the safety of that activity is sufficient to stop it from taking place."[18]

American officials have sometimes been skeptical of the precautionary principle, favoring a cost-benefit approach to regulatory problems. But in many cases, American law itself seems to follow the precautionary principle. The most prominent example is the ambient air quality provisions of the Clean Air Act, which require EPA to build an "adequate margin of safety" into standard-setting. Courts have enthusiastically approved agency decisions that are based not on demonstrated harm, but on a range of conservative assumptions. As we have seen, the EPA's assumption of a linear non-threshold model is explicitly defended on precautionary grounds. And in numerous contexts, that model has been crucial to regulatory decisions.

B. Difficulties

It is tempting to complain that the precautionary principle is vague. Suppose that regulators accept the precautionary principle; if so, exactly how precautionary should they be? If adverse effects are demonstrated from occupational exposure to benzene at 50 parts per million (ppm), and if the shape of the dose-response curve is unknown, should they impose a ceiling of 20 ppm, or 10 ppm, or 5 ppm, or 1 ppm? By itself the precautionary principle cannot answer this question. It is also tempting to object that the precautionary principle would impose excessive costs. Imagine a proposal to regulate arsenic in drinking water with a maximum exposure limit of 3 parts per billion. Might it not be relevant if the cost of such a proposal would be $750 million per year? Among those subject to regulation, the precautionary principle tends to be anathema, simply because it raises the spectre of draconian regulation. In these circumstances, cost-benefit balancing might well seem preferable.

But our goal here is to focus on an analytically prior question: Is the precautionary principle even coherent? In some cases, it appears not to be; it forbids all courses of action, including regulation, inaction, and everything in between. The reason is that risks are on all sides of social situations. Most of the time, regulation of risks itself imposes risks, and therefore runs afoul of the precautionary principle. For the principle to give the appearance of coherence, regulators must focus on a subset of the risks at stake and ignore the rest. But why would a sensible regulatory agency adopt that form of selectivity?

Consider a few examples. It is tempting to say (and it is standardly said) that the precautionary principle calls for strong controls on arsenic, on genetic engineering of food, on greenhouse gases, on threats to marine mammals, and on nuclear power. In all of these cases, there is a possibility of serious harms, and no authoritative scientific evidence suggests that the possibility is close to zero. If the burden of proof is on the proponent of the activity or processes in question, the precautionary principle would seem to impose a burden of proof that cannot be met. Put to one side the question of whether the precautionary principle, understood to compel stringent regulation in these cases, is sensible. Let us ask a more fundamental question: Is that more stringent regulation therefore compelled by the precautionary principle?

The answer is that it is not. In some of these cases, it should be easy to see that in its own way, stringent regulation would actually run afoul of the precautionary principle. The simplest reason is that such regulation might well deprive society of significant benefits, and for that reason produce a large number of deaths that would otherwise not occur. In some cases, regulation eliminates the "opportunity benefits" of a process or activity, and thus causes preventable deaths. If this is so, regulation is hardly precautionary. The most familiar cases involve the "drug lag," produced by a highly precautionary approach to the introduction of new medicines and drugs into the market. If a government takes such an approach, it might protect people against harms from inadequately tested drugs; but it will also prevent people from receiving potential benefits from those very drugs. Is it "precautionary" to require extensive premarketing testing, or to do the opposite?

Or consider the continuing debate over whether

certain antidepressants impose a (small) risk of breast cancer.[19] A precautionary approach might seem to caution against use of such antidepressants because of their carcinogenic potential. But the failure to use those antidepressants might well impose risks of its own, certainly psychological and possibly even physical (because psychological ailments are sometimes associated with physical ones as well). Or consider the decision, by the Soviet Union, to evacuate and relocate more than 270,000 people in response to the risk of adverse effects from the Chernobyl fallout. It is not clear that on balance, this massive relocation project was justified on health grounds: "A comparison ought to have been made between the psychological and medical burdens of this measure (anxiety, psychosomatic diseases, depression and suicides) and the harm that may have been prevented."[20] More generally, it is possible that a sensible government ignores the small risks associated with low levels of radiation, on the ground that precautionary responses are likely to cause fear that outweighs any health benefits from those responses.[21]

Or consider the case of genetic modification of food. Many people believe that a failure to allow genetic modification might well result in numerous deaths, and a small probability of many more.[22] The reason is that genetic modification holds out the promise of producing food that is both cheaper and healthier – resulting, for example, in "golden rice," which might have large benefits in developing countries.[23] Now the point is not that genetic modification will definitely have those benefits, nor that the benefits of genetic modification outweigh the risks. The point is only that if the precautionary principle is taken literally, it is offended by regulation as well as by nonregulation. So too for regulation of ground-level ozone. Such regulation does seem justified by the precautionary principle, for responsible people believe that low levels of ozone produce a range of health harms, including risks of death.[24] But there is also evidence that ground-level ozone produces health benefits, by reducing risks of cataracts and skin cancer.[25] Because the precautionary principle calls for protection when causal connections are unclear, it would appear to require, with respect to ground-level ozone, both stringent regulation and no regulation at all.

Sometimes regulation would violate the precautionary principle because it would give rise to substitute risks, in the form of hazards that materialize, or are increased, as a result of regulation. Consider the case of nuclear power. It is reasonable to think that in light of current options, a ban on nuclear power will increase dependence on fossil fuels, which contribute to global warming. If so, such a ban would seem to run afoul of the precautionary principle. Or consider the EPA's effort to ban asbestos, a ban that might well seem justified or even compelled by the precautionary principle. The difficulty, from the standpoint of that very principle, is that substitutes for asbestos also carry risks. Or consider possible risks to marine mammals from the United States Navy. Some people are concerned that efforts to eliminate those risks will endanger military preparedness, if only because of administrative barriers to training exercises. In these circumstances, what is the appropriate approach, according to the precautionary principle? The problem is pervasive, for opportunity benefits and substitute risks are the rule, not the exception.

It is possible to go much further. A great deal of evidence suggests the possibility that an expensive regulation can have adverse effects on life and health.[26] It has been urged that a statistical life can be lost for every expenditure of $7 million[27]; it has also been estimated that the requisite expenditure, for a loss of life, is $50 million[28]; and one of the most careful studies suggests a cutoff point, for a loss of life per regulatory expenditure, of $15 million.[29] A striking study suggests that poor people are especially vulnerable to this effect – that a regulation that reduces wealth for the poorest 20% of the population will have twice as large a mortality effect as a regulation that reduces wealth for the wealthiest 20%.[30] To be sure, both the phenomenon and the underlying mechanisms are disputed.[31] We do not mean to accept any particular amount here, or even to suggest that there has been an unambiguous demonstration of an association between mortality and regulatory expenditures.[32] The only point is that reasonable people believe in that association. It follows that a multimillion dollar expenditure for "precaution" has — as a worst case scenario — significant adverse health effects, with an expenditure of $200 million as leading to perhaps as many as thirty to forty lives lost.

This point makes the precautionary principle hard to implement not merely where regulation removes "opportunity benefits," or introduces or increases substitute risks, but also in any case in which the regulation costs a significant amount. If this is so, the precautionary principle, for that very reason, seems to argue against many regulations. If the precautionary principle argues against any action that carries a small risk of significant harm, then we should be reluctant to spend a lot of money to reduce risks, simply because those expenditures themselves carry risks. Here is the sense in which the precautionary principle, taken for all that it is worth, is paralyzing: It stands as an obstacle to regulation and nonregulation, and to everything in between.

Is there anything that advocates of the precautionary principle might say or do by the way of response? At first glance, the goal should be to apply the principle in a way that is alert to the full range of risks at stake. Perhaps regulators should take precautions against those risks that are most supported by evidence; perhaps they should take special steps against risks that might be grave or catastrophic, or that threaten to produce irreversible harm. It would certainly be plausible to create a distinctive "margin of safety" for potentially catastrophic risks. Refinement of the precautionary principle would call for a great deal of further work. Let us explore the particular challenge posed by hormesis.

III. Hormesis and Precautions

A. Definitions and Evidence

Hormesis, a Greek term meaning "to excite,"[33] generally describes the salutary effects that toxic chemicals may exhibit at low doses. Hormesis is not a new phenomenon. In 1888, German pharmacologist Hugo Shulz observed that small doses of poisons appeared to stimulate the growth of yeast.[34] Schulz also studied the work of Rudolph Arndt, who had carried out animal studies of drugs at low doses.[35] These early studies suggested the presence of hormetic effects. While the science lost credibility between the 1920s and the 1930s because of its association with homeopathy, it has recently regained status within the scientific community.[36]

The technical definition of hormesis describes the stimulatory process that happens at low doses: "Hormesis should be considered an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response." [37] According to existing research, a substance may provoke a hormetic response in one of two ways: either "1) the toxin directly induces a hormetic response [direct stimulation hormesis (DSH)], or 2) the toxin initiates a biological process that follows an initial disruption in homeostasis [overcompensation stimulation hormesis (OCSH)]."[38] Both types of hormesis – DSH and OCSH – may be graphically depicted as U-shaped (or j-shaped) dose response curves.[39]

DSH occurs when an adaptive response brings about a metabolic excursion. The organism experiences no damage; instead, the process represents an invariable response.[40] OCSH, in contrast, occurs as a reaction to low levels of stress or damage to the organism. Much like a vaccine, it results in enhanced fitness for some physiological systems for finite periods of time, or, in some cases, indefinitely.[41] Primary conceptual features of OCSH include the disruption of homeostasis, modest overcompensation, the reestablishment of homeostasis, and the adaptive nature of the process.[42] OCSH allots resources initially allocated for repair activities elsewhere so as to protect against subsequent invasions, or to be employed for other useful functions.[43]

Edward J. Calabrese and Linda A. Baldwin have found features of hormetic dose-response relationships to be widespread and generalizable.[44] Indeed, several recent studies note the pervasiveness of hormesis in toxicology. In one such study, Calabrese studied dose-response curves already present in the published toxicological literature.[45] Out of 664 dose-response relationships, he found that hormetic dose-response curves outnumbered curves showing no effect at the lowest doses by a ratio of 2.5 to 1.[46] Overall, Calabrese estimates that a U-shaped (or j-shaped) dose-response relationship may be reliably expected in about 40% of experiments with appropriate study design.[47]

In terms of particular chemicals, low levels of substances such as cadmium, dioxin, saccharin, polycyclic aromatic hydrocarbons, and certain gamma-ray sources have been shown to reduce tumors in some species.[48] Inorganic agents, such as arsenic, lead, mercury, selenium, and zinc, have demonstrated similar effects.[49] Low doses of X-rays have prolonged lifespan for mice and guinea pigs, acetaldehyde has enhanced longevity in fruit flies, multiple stressor agents have extended longevity in nematodes, and lead has enhanced growth in various plant species.[50] Low or modest consumption of ethanol, it is argued, reduces total mortality in humans.[51] Radiation has displayed hormetic effects as well.[52]

Some hormetic effects are quite complex, and the complexities have a clear bearing on regulatory policy and the question of precautions. While some evidence implies that dioxin suppresses breast tumors at low doses, studies have also shown that small amounts of dioxin can promote liver tumors; only when all tumors are taken into account do the dioxins exhibit a U-shaped curve.[53] Cadmium fits this profile as well; small doses could help prevent some cancers, but they may promote other kinds of cancers.[54]

B. Precautionary Defaults?

As we have noted, both types of hormesis – DSH and OCSH – may be graphically depicted as a U-shaped (or j-shaped) dose-response curve.[55] A U-shaped curve challenges several aspects of current EPA practice. EPA now uses two default dose-response models to extrapolate risk.[56] When assessing non-carcinogenic risks, the EPA uses the threshold model. This model finds an assumed toxicological threshold dose, called the "no observed adverse effect level" ("NOAEL"), and regulates dose amounts greater than this. When assessing carcinogenic substances, the EPA uses the linear non-threshold model. This model assumes that the substance demonstrates no safe level of exposure.[57] For physical and chemical exposure to carcinogenic substances, the EPA assumes that all exposures, even those in extremely low doses, carry an associated cancer risk.

Agencies use default options to bridge uncertainties in risk assessment when the assessment encounters 1) missing or ambiguous information with regards to a particular substance, or 2) gaps in current scientific theory.[58] Because science has been unable to determine risk levels at extremely low doses, an assumed low-dose linearity would appear rational and consistent with the health and safety goals of environmental protection. Standard arguments in support of the use of the linear model include plausibility and simplicity.[59]

But hormesis directly challenges both default assumptions, most significantly the linear non-threshold model. Agencies have historically preferred to err on the side of protecting public health in the face of uncertainty. This is an American application of the central idea of precaution. Even if we lack authoritative evi-

dence of a risk, its possibility may remain enough to mandate investment in prevention as a kind of regulatory insurance. The idea has received official endorsement from the Supreme Court, which noted in the highly influential *Benzene* case: "[S]o long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions in interpreting the data."[60] The Court went further still, indicating that the agency should risk "error on the side of overprotection rather than underprotection."[61]

But which approach risks what kind of problem? Taking hormesis into account severely complicates the EPA's approach and even its claims to be precautionary. If the EPA currently assumes that the linear non-threshold model is conservative – meaning that it errs on the side of protecting public health – and we find that toxins benefit human health at low doses, then the model has it backwards. In fact, the act of eliminating low doses could compromise public health. When hormesis is involved, use of a linear dose-response curve, without safe thresholds, will actually cause mortality and morbidity effects. There is no simple answer to the question of which default approach is precautionary. To raise this question is not to take any stand on whether some, many, or all toxic agents are beneficial or instead harmful at very low doses. It is only to say that the simultaneous possibility of benefits at low levels and of harms at low levels makes the precautionary principle exceedingly difficult to apply.

The general conclusion is clear. In light of the possibility of hormesis, the precautionary principle, in its simplest form, does not justify any particular default assumption. A linear non-threshold model is both compelled by the principle and forbidden by it. It is compelled by the principle because of the possible risk of harm at low levels; it is forbidden by the principle because of the possibility of benefit at low levels (and hence the possibility of harm from eliminating low levels of exposure). There is no reason to focus only on the risks of inaction and to neglect the risks of action. Here, then, is a specific example of our general suggestion about the precautionary principle: It can be made operative only if regulators blind themselves to many aspects of a situation and focus on a subset of the risks at stake. If hormesis is possible, then a linear dose-response curve, without thresholds, might not be precautionary at all.

IV. Precaution and Defaults: Policy and Law

A. EPA

What might sensible regulators do? If full information were available, they should identify the magnitude of the relevant risks and select an approach that improves human health on balance. The problem of course is that EPA lacks full information. EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment, which extend the existing 1986 Guidelines for Carcinogen Risk Assessment, attempt to make progress in the face of uncertainty. As stated in a proposed rule, "[T]he 1986 EPA guidelines reflect the position of the Office of Science and Technology Policy that '[N]o single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanisms of action exists . . . the models or procedure employed should be consistent with the evidence.'" The 1986 guidelines encourage case-by-case assessments so as to decipher the suitability of a particular extrapolation model. The agency explains: "When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a low-dose extrapolation model other than the linearized multistage procedure might be considered more appropriate on biological grounds."[63] The guidelines make clear, however, that "[w]hen a different model is chosen, the risk assessment should clearly discuss the nature and weight of evidence that led to the choice."[64]

The recent revised guidelines continue to endorse what EPA describes as a "conservative" approach to public health, with some modifications.[65] The 1996 proposed rules investigate two apparently plausible views about when to depart from a default.[66] The first view, "plausible conservatism," urges that departures from defaults should not be made unless new information improves the understanding of a biological process to the point that experts concur that the conservative default assumption is no longer plausible.[67] The second view, known as the "maximum use of scientific information" approach, agrees that the initial choice of default should be conservative but urges that conservatism should not be a factor in determining whether to depart from the default.[68] Rather than require that experts prove the default assumption implausible, this second view argues that risk managers need only find the alternate approach more plausible than the default.[69]

The EPA has adopted neither view. Instead, EPA states:

> "The decision to use a default, or not, is a choice considering available information on an underlying scientific process and agent-specific data, depending on which kind of default it is. Generally, if a gap in basic understanding exists, or if agent-specific data are missing, the default is used without pause. If data are present, their evaluation may reveal inadequacies that also lead to use of the default. If data support a plausible alternative to the default, but no more strongly than they support the default, both the default and its alternative are carried through the assessment and characterized for the risk manager. *If data support an alternative to the default as the more reasonable judgment, the data are used.*"[70]

Finally, if the default concerns an inherently complex biological question, then the EPA will require a large amount of data in order to replace the default.[71] In sum, if data reveal both a biologically reasonable mecha-

nism of action, and appear persuasive as applied to the case at hand, then the EPA will agree to stray from its default.

To say the least, this standard is not transparent. The EPA appears to say that in general, the default should be rejected if evidence so suggests – but in the context of great complexity, there is a strong presumption in favor of the default. How has the EPA's standard been applied? Consider an example. In 2000, the EPA promulgated a final rule limiting, *inter alia*, radionuclides in drinking water.[72] During the notice-and-comment period, parties challenged 1) the use of a linear, non-threshold model for radiation, 2) EPA's failure to find a threshold for radium, and 3) EPA's failure to promote claimed beneficial effects of ionizing radiation – to recognize hormesis – in its analysis. [73]

First, EPA concluded that a linear, non-threshold model remains appropriate for radiation, especially given several studies showing that a single radiation track traversing a cell nucleus might cause DNA lesions and chromosomal aberrations.[74] Second, the agency rejected the claim that radiation exhibits a "practical threshold" with regards to cancer; if a threshold exists, it would only apply to bone cancer, and not to other types of cancer.[75] Third, the agency ruled hormetic principles irrelevant to environmental radiation protection, as they had not been shown to occur at environmental dose levels: "[H]ormesis has not been demonstrated in normal healthy active populations of mammals, much less in humans."[76] Finally, EPA concluded that hormesis and adaptive response principles describe non-specific phenomena that merely remain the results of stress.[77] If toxicants stimulated the immune system generally, then there would be little, if any, benefit to hormesis for human beings who live in the world and are exposed to background toxins daily.[78]

B. Hormesis and Scientific Uncertainty

As a purely descriptive matter, EPA appears to be skeptical of hormesis as a basis for regulatory policy. But this judgment depends on its reading of the scientific literature, and if the scientific consensus changes, then the agency should be expected to change as well. There are a number of obstacles to its doing so. While hormesis has gained increasing attention from the scientific community, the idea has not received universal acceptance.[80] Many toxicological experiments do not allow assessment of possible hormetic dose responses.[81] The maximum stimulatory response with a U-shaped dose-response is often only 30-60% greater than control; hence, the issue of statistical power remains extremely critical in hormetic studies.[82] In addition, there have been direct challenges to the hormetic hypothesis. In a 1997 study, reproductive biologist Frederick vom Saal discovered that low levels of bisphenol-A, which is used in making plastics, enlarged prostate glands in the male offspring of pregnant mice.[83] Other experiments have similarly found that toxins can trigger adverse effects at low doses.[84] Recently, for example, toxicologist Tyrone Hayes found that exposure to small doses of atrazine correlated with reproductive deformities in frogs.[85] Another wave of studies found that endocrine disruptors may be more harmful at small doses than they are at larger doses.[86]

Adverse effects have also been associated with hormetic effects. For example, a chemotherapeutic drug that is effective at high doses (due to inhibitory effects on cell proliferation) may be harmful at lower doses, where it may stimulate cell proliferation and promote tumor growth.[87] In the case of a hormetic antibiotic, a high dose may kill bacteria, permitting the patient to survive, whereas lower doses may enhance the survival of the bacteria, to the detriment of the patient.[88] Subsections of the population might be especially sensitive to chemicals, even to hormetic toxins at low doses.[89] For example, babies and individuals with AIDS or genetic defects may suffer from undeveloped or compromised immune systems.[90]

C. Legal Challenges?

Suppose that the EPA, or some other agency, chooses a linear, nonthreshold dose-response curve in deciding how much to regulate – and contends that this approach is precautionary and legitimate as such. Suppose that the agency's decision is challenged as unlawful. How will the legal claims be assessed?

The first question is whether the agency has violated the statute it is supposed to administer. In resolving that question, courts will first ask whether Congress has "directly decided the precise question at issue" – whether the legislature has unambiguously banned what the agency proposes to do.[91] If the answer is no, then courts will ask whether the agency's interpretation of the statute is reasonable or instead "bizarre."[92] So long as the agency has not interpreted the statute in a way that plainly violates it, or makes no sense, the agency is highly likely to prevail.

Its decision might also be challenged as arbitrary and capricious under the Administrative Procedure Act. In assessing this challenge, the question is not whether the statute has been violated; it is whether the agency has been arbitrary in its assessment of the evidence, a question to which hormesis is plainly relevant.

Under this framework, proponents of hormesis might challenge EPA rulemaking on several fronts. First, they might assert that EPA has not used the best available science, as required by several statutes. Second, they might contend that, based on hormetic principles, the toxin's risk is *de minimus* and therefore not regulable. Third, they might argue that EPA has not properly weighed the costs and benefits of regulation.

1. Best Available Science

The Safe Drinking Water Act ("SDWA") provides

that, "to the degree that an agency action is based on science, the Administrator shall use — (i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods . . . ."[93] In interpreting this mandate, courts have required only that EPA use the best science available to it *now*, not that EPA take into account science that will potentially be available in the future. A comparison of two cases – *Waukesha v. EPA*[94] and *Chlorine Chemistry Council v. EPA*[95] – is instructive here. These are the cases in which dose-response curves have been most plainly at issue in the federal courts.

In *Waukesha v. EPA*, the D.C. Circuit upheld EPA's use of a linear nonthreshold model where the model represented the best science currently available. Under the SDWA, EPA is to promulgate standards called maximum contaminant levels ("MCLs") that cap the quantity of contaminants permitted in drinking water from public water systems. Industry petitioners urged that the EPA had not based the MCLs on the "best available science" as required by the statute. They argued that the data required the use of a quadratic dose-response curve for bone cancer, one based on a "model which assumes that the excess risk is proportional to the square of the dose, meaning that low dosage presents no appreciable cancer risk."[96]

The court held that the agency had sufficiently justified its choice of dose extrapolation model. First, EPA had concluded that the data suggesting threshold effects were "of limited value for the estimation of risk" because reliability problems, including radium dosimetry, the high mortality rate in some groups, and, in particular, the small number of subjects at low dose levels, impaired the threshold data's usefulness for constructing a dose-response relationship. The court also noted that, generally speaking, "the linear non-threshold approach is universally used for assessing the risk from environmental exposure to radionuclides as well as other carcinogens."[97] In the meantime, the EPA was to continue to research the issue: as its final rule stated, "EPA is actively supporting national and international studies of radiation dosimetry and dose reconstruction, radionuclide biokinetics, quantitative techniques for uncertainty analyses, and long-term follow-up epidemiological studies of populations exposed chronically to low-dose radiation."[98]

The *Waukesha* court distinguished the case at hand from that of *Chlorine Chemistry Council v. EPA*.[99] In *Chlorine Chemistry Council*, the court found that the EPA's use of a default assumption of linearity and zero MCLG violated the SDWA because it "openly overrode the 'best available scientific evidence'" at the time of the rulemaking – the science that suggested that chloroform is a threshold carcinogen.[100] In contrast with the situation in *Waukesha*, EPA had previously found, and had conceded openly during the course of litigation, that exposures to chloroform below a threshold level posed no risk of cancer. The court therefore ruled EPA's rulemaking arbitrary and capricious. "All scientific conclusions are subject to some doubt," and "future, hypothetical findings always have the potential to solve the doubt."[101] What is significant, the court stated, is Congress' requirement that the action be based upon the best available evidence at the time of the rulemaking: "The word 'available' would be senseless if construed to mean 'expected to be available at some future date.'"[102]

These decisions suggest that under statutes that require the "best science," agency decisions will be vulnerable if they disregard hormesis under circumstances in which existing scientific understandings make the agency's judgment unreasonable. In addition, an agency's refusal to consider hormesis will likely be arbitrary if EPA has evidence of hormetic effects at the time of rulemaking. In the face of doubt among experts, the EPA will have the authority to consider hormesis or not as it chooses. In any case, EPA must give a reasoned explanation for its decision to proceed in one way rather than another.

2. De Minimis Risk

A petitioner may also use hormesis to argue that a risk is *de minimis* rather than significant. Under *Chemical Manufacturers' Association v. EPA*, regulation must deliver significant benefits.[103] This idea limits the reach of the precautionary principle. If EPA considers hormetic effects, then more risks will likely be considered *de minimis*.

The *Benzene* case provides guidance in this regard.[104] In that case, the Supreme Court concluded that an agency must show that a risk that it intends to regulate is "significant." The "significant risk" requirement now governs agency decisions under the Occupational Safety and Health Act, and it plays an important role under other statutes as well. As discussed above, the precautionary principle appears to counsel an agency to assume, in the absence of data, that a LNT model would be the most protective of human health. But this is a misreading of the very idea of precaution. And if an agency has actual data in support of a hormetic effect, a party might be able to challenge the use of the default extrapolation on the ground that it calls for regulation of a risk that is trivial or nonexistent.[105]

3. Risk-Risk Tradeoffs, Costs vs. Benefits

Many statutes (including, for example, certain sections of the CAA[106] and the Toxic Substances Control Act[107]) require comparison of relevant risks or consideration of costs and benefits. Hormesis would shift the agency's assessment, as it would add additional benefits.

Under the linear nonthreshold paradigm, default risk analysis assumes that exposure to toxic chemicals conveys no health benefit.[108] But a number of judicial decisions encourage agencies to engage in "risk-risk tradeoffs," by comparing the risk reduction pro-

duced by regulation with the risks created by regulation.[109] If regulation threatens to eliminate a health benefit, the agency might well be required to take that fact into account. An analogy to *American Trucking Association v. EPA*[110] ("*ATA I*") is in order here.

In *ATA I*, the D.C. Circuit accepted a legal challenge to an environmental regulation based upon the agency's failure to consider a risk-risk tradeoff under Sections 108 and 109 of the Clean Air Act ("CAA").[111] Section 109 of the statute requires that the EPA base its promulgation of national ambient air quality standards ("NAAQS") upon published "criteria" that, according to Section 108, reflects the "latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare," from the relevant pollutants.[112] Challenging EPA's interpretation, industry petitioners urged that the EPA had failed to account for the potentially beneficial effects of tropospheric ozone, including shielding people from ultraviolet rays, when it considered the harmful effects of radiation.[113] According to the petitioners, the "all identifiable effects" language embraced both the negative and the positive effects of a regulated pollutant. The agency understood the requirement to refer to the effects of substances as "pollutants," and not insofar as they produced health benefits. Refusing to defer to the agency, the D.C. Circuit found the administrative interpretation strange: "It seems bizarre," wrote Judge Williams, "that a statute intended to improve human health would, as 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."[114]

In this light, a court may very well consider a refusal to weigh a scientifically accepted hormetic benefit as "bizarre" under the CAA and similar statutory schemes. The result would be to shift the weighing of costs and benefits – and possibly to do so significantly.

CONCLUSION

The precautionary principle is designed to give safety the benefit of the doubt – to create margins of safety against risks that may or may not materialize. We have seen that the principle runs into serious difficulty when risks are on all sides of the relevant situation. Sometimes regulation itself produces safety or health hazards, as, for example, by giving rise to substitute risks or by eliminating the benefits that might come from an activity or process. For toxic substances, hormesis much complicates the operation of the precautionary principle, simply because aggressive regulation might cause adverse health effects, rather than reducing them. When hormesis is possible, the precautionary principle both requires and condemns the use of a linear non-threshold model.

To decide what to do, regulators must go beyond the precautionary principle; it is unhelpful and even incoherent for agencies to attempt to be precautionary. The only sensible approach is to use the best scientific understandings of relevant risks and to adopt sensible default assumptions in the face of uncertainty. In some contexts, the linear non-threshold model will come under significant pressure as a matter of policy and law. The extent of the pressure should be resolved by the extent of the evidence, not by an injunction to adopt precautions. This point seems to us to offer a large and quite general lesson for regulatory policy.

NOTES

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3. See, e.g., American Petroleum Inst. v. OSHA, 581 F.2d 493, 504n.24 (5th Cir. 1978), aff'd, Benzene, 448 U.S. 607 (1980) ("Generally, exposure to higher levels carries with it a higher risk, and exposure to lower levels is accompanied by a reduced risk.")
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6. For an interesting discussion, see Frank B. Cross, Legal Implications of Hormesis, available at http://www.belleonline.com/home92.html
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9. Quoted in Rethinking Risk and the Precautionary Principle 3, Julian Morris ed. (2000).
10. Quoted in Bjorn Lomborg The Skeptical Environmentalist 347 (2001).
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12. See http://www.monitor.net/rachel/r586.html

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14. See Bjorn Lomborg The Skeptical Environmentalist 348 (2001).
15. http://www.logophilia.com/WordSpy/precautionaryprinciple.asp
16. Testimony of Dr. Brent Blackwelder, President, Friends of the Earth, before the Senate Appropriate Committee, Subcommittee on Labor, Health and Human Services (Jan. 24, 2002).
17. See Goklany, supra note, at 6.
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36. Id. See also Edward J. Calabrese, "Hormesis Revisited: New Insights Concerning the Biological Effects of Low-Dose Exposures to Toxins," 27 Envtl. L. Rep. 10526 (1997).
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48. Edward J. Calabrese and Linda A. Baldwin, "Toxicology Rethinks Its Central Belief," 13 Nature 691 (2003).
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53. Kaiser, "Sipping From a Poisoned Chalice" at 379, supra note.
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93. Safe Drinking Water Act, 42 U.S.C. § 300g-1(b)(3)(A)(2003). See also Occupational Safety and Health Act, 29 U.S.C. § 655(b)(5) (Administrator must set standards "on the basis of the best available evidence").
94. Waukesha, 320 F.3d at 228.
95. Chlorine Chemistry Council v. EPA, 206 F.3d 1286 (D.C. Cir. 2000).
96. Waukesha, 320 F.3d at 249.
97. Id. at 250.
98. 65 FR at 76721, supra note 7.
99. Chlorine Chemistry Council, 206 F.3d at 1286 (internal citation omitted).
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101. Id.
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opinion in Benzene).

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106. See, e.g., 42 U.S.C. § 7545(c)(2)(B).

107. See Corrosion Proof Fittings v. EPA, 947 F.2d 1201 (5th Cir. 1991) (holding that TSCA requires aggressive cost-benefit balancing).

108. Lave, "Hormesis: Policy Implications" at 141, supra note 50.

109. See Cost-Benefit Default Principles, supra note.

110. ATA I, 175 F.3d at 1027 (D.C. Cir. 1999).

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PRECAUTIONARY PRINCIPLES: A JURISDICTION-FREE FRAMEWORK FOR DECISION-MAKING UNDER RISK

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ABSTRACT

Fundamental principles of precaution are legal maxims that ask for preventive actions, perhaps as contingent interim measures when relevant information about causality and harm remains unavailable, to minimize the societal impact of potentially severe or irreversible outcomes. Such principles do not explain *how* to make choices or how to identify what is protective when incomplete and inconsistent scientific evidence of causation characterizes the potential hazards. Rather, they entrust lower jurisdictions, such as agencies or authorities, to make current decisions while recognizing that future information can contradict the scientific basis that supported the initial decision.

After reviewing and synthesizing national and international legal aspects of precautionary principles, this paper addresses the key question: How can society manage potentially severe, irreversible or serious environmental outcomes when variability, uncertainty, and limited causal knowledge characterize their decision-making? A decision-analytic solution is outlined that focuses on risky decisions and accounts for prior states of information and scientific beliefs that can be updated as subsequent information becomes available. As a practical and established approach to causal reasoning and decision-making under risk, inherent to precautionary decision-making, these (Bayesian) methods help decision-makers and stakeholders because they formally account for probabilistic outcomes, new information, and are consistent and replicable.

Rational choice of an action from among various alternatives – defined as a choice that make preferred consequences more likely – requires accounting for costs, benefits and the change in risks associated with each candidate action. Decisions under any form of the precautionary principle reviewed must account for the contingent nature of scientific information, creating a link to the decision-analytic principle of expected *value of information* (VOI), to show the relevance of new information, relative to the initial (and smaller) set of data on which the decision was based. We exemplify this seemingly simple situation using risk management of BSE. As an integral aspect of causal analysis under risk, the methods developed in this paper permit the addition of non-linear, hormetic dose-response models to the current set of regulatory defaults such as the linear, non-threshold models. This increase in the number of defaults is an important improvement because most of the variants of the precautionary principle require cost-benefit balancing. Specifically, increasing the set of causal defaults accounts for beneficial effects at very low doses. We also show and conclude that *quantitative* risk assessment dominates *qualitative* risk assessment, supporting the extension of the set of default causal models.
Key Terms: precautionary principles, legal and scientific causation, scientific and legal evidence, probabilities, hormesis, value of information

INTRODUCTION

We contribute a legal-scientific analysis of *whether non-linear (e.g., biphasic) dose-response models are now ripe for inclusion, and thus should be included, in the set of regulatory dose-response defaults*, within the context of *implementing* precautionary principles. These are relatively new legal maxims that impose a complex balancing of risks, economic and social costs and benefits, under uncertain and contingent decision-making. At the outset, we note the fundamental difference between legal principles and scientific principles. Although a legal maxim is a general legal statement not used as a court's rationale for its decision, it is a statement of either equity or fairness.[1] On the other hand, a scientific principle, such as Heisenberg's Uncertainty Principle, is a fundamental scientific truth. Understanding precautionary principles goes beyond their lexical analysis. It is a legal and scientific enquiry, from the laws of European and international jurisdictions to the assessment of hazardous situations potentially causing severe or irreversible outcomes from the perspective of:

1. Alternative forms of precautionary principles, as enunciated in Treaties, Conventions, and case law,
2. Legal causation and degrees of legal proof implied by them,
3. A formal, scientific causal network consistent with 1 and 2, and

4. A discussion of quantitative and qualitative risk methods.

Roush (2002) places our work, and the essence of current debates, in an historical context. He recounts that:

> "When a Bill was introduced for the Liverpool-Manchester railway in 1825, it was defeated … it was said that the railway would 'prevent cows grazing and hens laying.' The poisoned air from the locomotives would kill birds as they flew over them and render the preservation of pheasants and foxes no longer possible. There would no longer be any use for horses; and if the railways extended, the species would become extinguished, and oats and hay would be rendered unsalable commodities. Boilers would burst and blow passengers to atoms.' Perhaps '[w]orse, when George Stephenson said he confidently expected the trains to travel at 20 miles an hour, he was told by the Bill's promoters that 'if he did not moderate his views and bring his engine within a reasonable speed, he would inevitably damn the whole thing and be himself regarded as a maniac fit for Bedlam.'"

Both of these arguments are precautionary but antithetic: one looks at hazards and economic costs, the other at the loss of profit. As we will demonstrate, both have a legal basis. We begin our analysis under the shadow of this still current fundamental difference.

SETTING THE STAGE

The Breadth of Principles of Precaution

Much has been written about the origins of precautionary principles and their historical genesis (Sand, 2000; Wagner, 2000; Applegate, 2000; Appell, 2001). We summarize the essence of the precautionary principle in terms of its two principal variants. One, the *relative* form, requires the explicit legislative balancing of risks (as a cost measured by a change in the cumulative probability distribution of adverse outcomes) with monetized cost and benefits. It is an overall economic balancing enabled through secondary legislation. The other variant, the *absolute* form, urges precaution when the magnitude of the potential adverse event is large or the adverse outcome is severe, even if the probability of that outcome is small or uncertain. This form does not ask for risk-cost-benefit balancing to justify a choice, out of the set of choices.

A well-known statement of the Precautionary Principle, based on cost-effectiveness analysis, is that:

> "Where there are threats of serious or irreversible damage, lack of full scientific certainty should not be used as a reason for postponing such measures, taking into account that policies and measures to deal with climate change should be cost-effective so as to ensure global benefits at the lowest possible cost (Article 3, Framework Convention on Climate Change)." (Emphasis added)

We also find that, at the other extreme, a definition of the precautionary principle in the Third Ministerial Declaration on the North Sea (1990) that is ***acausal:***

> "Applying the precautionary principle, … is to take action to avoid potentially damaging impacts of [toxic] substances... even where there is no scientific evidence to prove a causal link between emissions and effects." (Emphasis added)

The California Environmental Protection Agency (Cal/EPA, 2003) Environmental Justice Advisory Committee (EJAC) recommended that Cal/EPA adopt the precautionary principle as a way to help promote environmental justice. It states that:

> "The EJAC reached broad consensus on the importance of using precautionary approaches to environmental and public health protection. Committee members believe that it is not necessary or appropriate to wait for actual, measurable harm to public health or the environment before evaluating alternatives that can prevent or minimize harm." (Emphasis added)

The CalEPA seems to limit the scope of the precautionary principle without *measurable harm* to the evaluation stage of decision-making. Thus, a potential state of future danger can trigger regulatory actions. The UK government prescribes a bounded role for precaution (Jordan and Riordan, 1998) that is consistent with cost-benefit analysis:

> "Where there are significant risks of damage to the environment, [we] will be prepared to take precautionary action to limit the use of potentially dangerous materials or the spread of potentially dangerous pollutants, even where scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it. The precautionary principle applies particularly where there are good grounds for judging either that action taken promptly at comparatively low cost may avoid more costly damage later, or that irreversible effects may follow if action is delayed."

Since at least the 1960s, Value of Information (VOI) analysis has been used in decision making under risk to clarify and guide decisions where current knowledge of the likely consequences of different actions (possibly including the "do nothing" or status quo option) is insufficient clearly to identify the best current action (Raiffa, 1968). Traditional decision analysis and risk-cost-benefit analysis do not necessarily urge delaying a decision until greater scientific certainty is available, as some proponents of the precautionary principle have seemed to imagine. Rather, they recommend identifying and taking the currently available action — which may range from doing nothing to intervening now to collecting more information before deciding — that makes preferred outcomes most likely (or, more precisely, maximizes the estimated expected utility of the probable consequences of current and future actions), as assessed using currently available information, however uncertain

and incomplete.

The social goal of prudently allocating scarce resources suggests that an open invitation to act without formal analysis of causation and likely consequences, and without explicit balancing of risks, costs, benefits, and uncertainties, can often be at least as damaging as no invitation at all. The prescription "do not just do something" without formal evaluation of the probable consequences of alternative decisions is reinforced by repeated experiences suggesting that well-intended, but under-analyzed, "precautionary" interventions — from requiring MTBE in gasoline to building sea walls to defend against storm surge to routinely prescribing antibiotics "just in case" (or, more recently, banning animal antibiotics to keep antibiotics working for human patients) — often exacerbate the very problems they are intended to prevent. The rational decision analysis paradigm quantifies and evaluates the probable consequences of actions. It uses current information and considers potential additional information, assessing whether information acquisition and waiting costs are less than the likely additional costs of deciding without it. On these grounds, decision analysis and VOI analysis are important tools for effective risk management when the causal link between actions and consequences is probabilistic.

As we will exemplify, a cost-benefit balancing does take place, implicitly or explicitly, whether or not the precautionary principles are used. Rationally, the balancing should be made explicit and take place openly, acknowledging and characterizing uncertainties, democratic decision processes that guide the final choice of precautionary, information-collecting, or other actions.

Risky Situations

Lofstedt (2002) discusses the implications of alternative versions of the precautionary principle on decision-making under *uncertainty*. He states three:

> "Version 1: Uncertainty does not justify inaction. In its most basic form, the precautionary principle is a principle that permits regulation in the absence of complete evidence about the particular risk scenario.
>
> Version 2: Uncertainty justifies action. …
>
> Version 3: Uncertainty requires shifting the burden and standard of proof. This version of the precautionary principle is the most aggressive. It holds that uncertain risk requires forbidding the potentially risky activity until the proponent of the activity demonstrates that it poses no (or acceptable) risk."

Because precautionary principles aim at potential *and* either grave (namely, serious) or irreversible outcomes, the necessary (but not sufficient) framework for implementing them is probabilistic.Specifically, a plausible taxonomy consists of:

> *Risky situation:* potential final outcomes are variable in magnitude and severity, with known or estimable probabilistic behavior & causal network relating exposure to response. For example, a hormetic dose-response and a linear, no-threshold model can be used in a risk assessment with probabilistic weights (as done in portfolio analysis and decision analysis) to weigh their importance to the analysis.
>
> *Ambiguous situation:* the state-of-knowledge about potential final outcomes is somewhere between risky and uncertain situations, which can be assessed using measures of ambiguity, possibility and account for fuzziness. For example, a decision-maker may select measures to represent lack of information that are not as crisp as probabilities.
>
> *Uncertain situation:* the potential outcomes are uncertain in magnitude, severity and causation, with unknown probabilistic behaviors & causation relating exposure to response. For example, a pure hypothetical situation formulated in the absence of an empirical basis and a causal link between exposure and response.

We exclude deterministic situations. In risky situations, subjective expected utility (SEU) theory provides one widely accepted, theoretically well-developed, normative framework for analysis. Under uncertainty, i.e., when probabilities cannot be assigned to potential events, analysts use different measures of uncertainty and adopt alternative forms of causal reasoning (e.g., Gilboa and Schmeidler, 2001).

Practically, precautionary principles deal with risky situations, which can be summarized (at some loss of generality) as *Risky A* and *Risky B*:

Risky A	Low probability hazards with consequences of large magnitude, M_i, high severity, S_i, risky causation. Residual risks may belong to Risky B, with uncertainty about the links between some aspects of the hazard and damage in the long term (e.g., cancer risk from low levels of exposure to fumes from and explosion; post-traumatic disorders …).
Risky B	Routine (low probability) hazards with consequences of low magnitude, m_i, high severity, s_i, spatially and temporally diffused hazards, source of the hazard can be difficult to identify. Causation is uncertain (linear, non-threshold or hormetic) at low dose or exposures. Generally, but not always, $E[\sum(m_i, s_i)] < \text{or} << E[\sum(M_i, S_i)]$.

Risky A situation. It requires separating the magnitude, say 500 prompt deaths from a catastrophic event, from the uncertainty about that particular number of death which is represented by a probability, say 1/100,000. It excludes basing a decision on the expected value of that outcome, $500*100{,}000^{-1} = 0.005$ prompt deaths, but asks instead for preventive action justified solely on the large number of potential deaths. In this situation, the mechanisms leading to catastrophic failure are known, although they can go unrecognized until after

the catastrophic event occurs. Next, suppose that a planned activity can cause either 500 cases of cancer with probability 0.001, or none at all, with probability 0.999, from a known causal occupational cancer-causing agent. The expected value of that loss is [(0.001*500)+(0.999 * 0.0)] = 0.5 excess cancer cases. Of course, either 500 excess case or 0 cases can occur: these two outcomes are mutually exclusive and fully exhaustive, under this example. If the alternative action to the one considered can be assessed just in terms of the expected magnitude of the adverse effect, the average number of cases, then 0.5 expected excess cases of cancer can be nearly trivial. A reason for such attitude may be that implementing an action to avoid 0.5 excess cancer cases could incur high costs. Its corollary issue is that increasing the number of potential outcomes requires a careful investigation of causation and probability assignments. For example, the case of 0 deaths with probability 0.10, 1.0 with probability 0.399, 5 with probability 0.5, and 1,000 with probability 0.001 is a situation likely to arise under the precautionary principle, and it is important to scrutinize the accuracy of the probability asserted to be 0.001. In the context of the precautionary principle, the dilemma should be resolved by the action that avoids the 500 excess cases of cancer. Probabilistic fault- and event-tree analysis generally provides the basis for assessing *Risky A situations*.

Risky B situation. The current concern with waterborne perchlorate in the environment (Urbansky, 2002; Renner, 2004, Christen, 2003; Hogue, 2003; The New York Times, March 3, 2004), a chemical primarily used in rocket fuel illustrates this situation. Traces of perchlorate, now reportedly found in most ground waters of the US, especially in the Southwest, occur in concentrations up to about 100 parts per billion (ppb). Exposure to low concentrations of perchlorate is associated with abnormal function of the thyroid, as well as other adverse health effects. The evidence of toxicological damage obtained from studying exposed rats, and applying a safety factor, has led the US EPA to consider a water quality standard for perchlorate at 1 ppb. On the other hand, the US DOD recommended a permissible exposure of 200 ppb, based on results in human adults. Both NASA and US DOD stated that the US EPA's work is "not based on good science" and is "scientifically unrealistic," respectively. Rebutting these, the US EPA states that it "has confidence in its work." The US Academies of Science, which has entered into the controversy, stated its role as "we don't try to eliminate bias. We try to balance it." Their report on perchlorate is due in 2004 and may result in a federal standard.

CAUSATION AND PROOF, some legal notions

A way to avoid the issues just exemplified is to place the burden of proof that a potential (proposed) activity is acceptably (or tolerably) risky, within the scope of current laws, on the party that benefits from it. In civil law, this is an exception to the general legal rule that a plaintiff (or intervenor) has that burden of proof about causation and damage. The rationale for this exception to the rule, under the precautionary principle, is that the proponent has superior knowledge, "deep pockets," and that the benefits accrue to that proponent. As an example of regulatory burden-of-proof shift, the EU Chemical White Paper (13 February 2001) states that:

> "Responsibility to generate knowledge about chemicals should be placed on industry. Industry should also ensure that only chemicals that are safe for the intended purposes are produced. The Commission proposes to shift responsibility to enterprises for generating and assessing data and assessing the risks of the use of the substances. The enterprises should also provide adequate information to downstream users."

In part to avoid spurious litigation, the EC's Commentary also states that:

> "A scientific evaluation of the potential adverse effects should be undertaken based on the available data ... [T]his requires reliable scientific data and logical reasoning, leading to a conclusion which expresses the possibility of occurrence and the severity of a hazard's impact on the environment, or health of a given population ..."

The Commentary then concludes that "precautionary measures must not be applied to address conjectured risks." Thus, at the policy level, the decision-maker would discard a true scientific conjecture. If so, this course of action would be consistent with the the Court of First Instance holding that:

> "It is necessary, first, to define the 'risk' which must be assessed when the precautionary principle is applied... A preventive measure cannot properly be based on a purely hypothetical approach to the risk, founded on mere conjecture which has not been scientifically verified ..."

The shift in the burden of proof has traditionally occurred in the US law when causation is ambiguous, as opposed to uncertain, and fairness requires the party that caused harm is punished. The shift is rebuttable. On this issue, the EU (EU, 2001) has stated that:

> "Community rules and those of many third countries enshrine the principle of prior approval (positive list) before the placing on the market of certain products, such as drugs, pesticides or food additives. This is one way of applying the precautionary principle, by shifting responsibility for producing scientific evidence. This applies in particular to substances deemed 'a priori' hazardous or which are potentially hazardous at a certain level of absorption. In this case the legislator, by way of precaution, has clearly reversed the burden of proof by requiring that the substances be deemed hazardous until proven otherwise. Hence it is up to

the business community to carry out the scientific work needed to evaluate the risk. As long as the human health risk cannot be evaluated with sufficient certainty, the legislator is not legally entitled to authorise use of the substance, unless exceptionally for test purposes."

We suggest that "sufficient certainty" is analogous to risky, but neither ambiguous or uncertain, situations. UK courts have rejected shifting the burden of proof[3] although Lord Wilbeforce made an unsuccessful attempt to reintroduce it in the McGhee case, decided in the House of Lords. It is yet unclear how the primacy of European law, as well as an eventual Constitution for the EU, squares with the UK's rejection (of reversing the burden of proof) because it raises significant conflict of laws, and thus becomes a limitation of the application of precautionary measures. Other High Courts, such as India's, have approved the shift in situations dominated by uncertain scientific causation involving precautionary actions. American courts have also shifted that burden in tort law since 1948[4], and thus provide the necessary – but not sufficient — jurisprudence on this issue. Shifting of the burden of proof is not just a legal issue. Rather, it potentially can affect health and incomes because a less stringent application of the same precautionary measures can – and often does – decrease the price of goods and services, thereby increasing the differential advantage that a country has relative to another. This discussion leads to the corollary question: Can we, at the highest level of abstraction, rely on qualitative, but causal, judicial findings of causation? These judgments are ultimately based on a weighing of the evidence through an omnibus test, which range from a finding of a (possibly unequivocal), substantial factor of injury, to clear and convincing evidence, all the way to beyond a reasonable doubt. The stringency of these tests increases from administrative to criminal adjudications.

Whither Objectivity, in Omnibus Legal Tests of Causation?

Most statements of the precautionary principle require a threshold of scientific causal knowledge that, when crossed, commands a public institution to provide a "high level of protection," in spite of uncertainty. To do so, that threshold must meet jurisdictionally different legal standards of causation. This causal threshold is determined by linking probable events within a scientific causal network, and then measuring it against legal causation (in tort law the difference is often stated as one between cause-in-fact versus proximate cause). The law uses seemingly objective tests of causation. Fundamentally, in civil cases in which the test used is strongly dependent on the jurisdiction where the case is heard, the law asks if the defendant's acts were a substantial factor in producing injury or whether, but for the defendant's actions, the plaintiff would not have suffered injury. The former compares the extent and importance of the defendant's activity in causing harm with other known and unknown causes. It is clearly subjective, and thus unlikely to produce predictable results in toxic exposure cases. The latter test (a logical true or false) limits evaluation of to the number of causal factors to one — it seeks to answer the statement "but for the act of the defendant the plaintiff would not have been injured."[5]

In the UK, legal causation has been assessed under a number of different forms: "real effective cause,"[6] "direct,"[7] "natural and probable,"[8] "proximate cause,"[9] and "caused or materially contributed to injury."[10] UK law, as *Reary and Hope v. British Nuclear Fuels plc*[11] indicates, generally requires an explanation of scientific causation based on balancing the probabilities that that a causal factor was related, through an epidemiological correlation, to adverse health outcomes, such as leukemia. The *Reary and Hope* court reviewed scientific causation basing its opinion on three of Hill's epidemiological criteria: strength of the association, as well as consistency and biological plausibility.

In Canada, causation is generally assessed under the "but for" test. More specifically, the Supreme Court of Canada, in *Snell v. Farrell* (1990) held that "causation is an expression of the relationship that must be found to exist between the … act … and the injury …" However, scientific evidence is not required when causation can be inferred from the physical facts, provided that that inference is not controverted. Fundamentally, there must be a proximate (legally sufficient) casual relation between an event and the damage that is stated to result from that event.

In the US, the Restatement Second of Torts uses "legal cause,"[12] which is predicated on determining whether an act is a "substantial factor"[13] in bringing about a bad result. The Restatement II considers, *inter alia*, the "number of factors", the conduct of the defendant in creating or setting in motion forces leading to injury, factors beyond the responsibility of the defendant, elapsed time, and the foreseeability between cause and effect.[14] The "substantial factor" test means that a sequential process of elimination isolates an eventually substantial one. Such a sequence requires a formal definition of what is a substantial factor because of its exclusionary role in building logically and legally defensible causation, thus avoiding arbitrariness, vagueness, and fuzziness. The search for a substantial factor, particularly for prospective actions, requires specific measures of uncertainty and a calculus. Furthermore, looking for a single substantial factor can be scientifically and legally naïve because two or more insubstantial factors can act synergistically and become equivalent to a single substantial factor. Because knowledge about measuring synergy is still in its infancy, a defendant may go unpunished. For either past or prospective legal decisions, developing the causal network requires a sound causal basis and a common measure of uncertainty, such as a probability, so that the magnitude of the belief in a factor being "substantial" can be reproduced. As always, one party can

assert that factor XYZ is substantial and attach to it a high probability (e.g., 0.99); the other can assett that the factor is not substantial, and attach to it a much lower value (e.g., 0.01). The balancing is done through the omnibus test used by the jurisdiction.

United States v. Fatico[15] suggests that the search for a judicially consistent threshold standard of proof – couched in qualitative terms — is doomed. In *Fatico*, Judge Weinstein polled several fellow judges in his federal district court to determine what probability values they assigned to four common legal tests (ranging from the *preponderance of the evidence to beyond a reasonable doubt*). Table 1 depicts the results.[16]

Table 1, Assessment of the Relationship between Four Qualitative Legal Tests and Probabilities

Judge number	Preponderance of the evidence (%)	Clear and convincing (%)	Clear, unequivocal, and convincing (%)	Beyond a reasonable doubt (%)
1	50+	60-70	65-75	80
2	50+	67	70	76
3	50+	60	70	85
4	51	65	67	90
5	50+	Elusive*	Elusive*	90*
6	50+	70+	70+	85
7	50+	70+	80+	95
8	50.1	75	75	85
9	50+	60	90	85
10	51	Not estimable**	Not estimable**	Not estimable**

* "Standard is elusive and unhelpful."
** "Cannot estimate numerically."

The numerical values of these fundamental legal tests are inconsistent and incoherent. For instance: if the balancing is 50%, then both sides are equipoised. More perplexing, the overlaps are inconsistent with the expressed scope of each test. *Fatico*'s findings are important for our work because the semantic vagueness and fuzziness at the boundaries of each test can lead to the wrong test being used unwittingly. Fatico attempts to explain why these standards are not correctly quantified. It cites Wigmore as a justification for lack of coherence: "no one has yet invented ... a mode of measurement for the intensity of human belief." It also quotes Starkie's doubt that "moral probabilities could ever be represented by numbers ... and thus subjected to arithmetical analysis …" and contrasts Starkie with Bentham's use of number to establish degrees of belief.

REGULATING PRECAUTION

Agencies or authorities interpret precautionary principles through secondary legislation, such as Directives or Regulations in the European Union (EU) or regulatory standards in the US. Those agencies then issue numerical standards or guidelines, after scientific peer review and public comments. The process and its outcome are legal, but they are based on the scientific method to justify a causal assertion between potential exposure and adverse outcome, which affects the choice of managerial action. Both process and standards can be reviewed, if a controversy arises about their appropriateness, at the administrative levels, then through the courts, and in the legislature. As an instance of legislative review, in American federal administrative and environmental law, there can be Congressional re-authorization after some specified period of time. In the EU, a new Treaty (or, when ratified, a true Constitution of the EU) can contain re-written Articles or have Articles deleted from the previous Treaty.

European Union

Article 130r (Title XIX, now renumbered as Art. 174) of the European Treaty of Union, Maastricht 1992, states the legislative – constitutional law — mandate for environmental protection for the EU as follows:

2. "Community policy on the environment shall aim at a high level of protection [and] shall be based on the precautionary principle. . ..
3. In preparing its policy on the environment, the Community shall take account of:
   i) available scientific and technical data;
   ii) environmental conditions in various regions of the Community;
   iii) the potential benefits and costs of action or lack of action;
   iv) the economic and social development of the Community as a whole and the balanced development of its regions.''

This Article also states that the European Community environmental protection objectives are:

i) preserving, protecting and improving the quality of

the environment;
ii) protecting human health;
iii) prudent and rational utilization of natural resources; and
iv) promoting measures at international level to deal with regional or worldwide environmental piroblems.

Acting notwithstanding uncertainty or risk is implicit in (i), *protection* is explicit in (ii) and *rational* decision-making is explicit in (iii). A measure of risk aversion is explicit in item (iii) through the term *prudent*. Objective (iv) implies the promotion of precautionary cooperation at an international level, which makes the analysis done in this paper even more cogent and necessary. The EU's form of the precautionary principle points to decisions justified by risk, cost, and benefits analyses: making rational decisions quantitatively balances "the potential benefits and costs of action or lack of action." In the EU, precautionary measures cannot be based on hypothetical risk or mere conjecture: these measures may be taken only if the risk appears to be adequately backed up by scientific data available.

The European Court of Justice's review of the EU Commission decision to ban export of beef from the United Kingdom to reduce the risk of BSE transmission (Judgements of 5 May 1998, cases C-157/96 and C-180/96) found that:

> "Where there is uncertainty as to the existence or extent of risks to human health, the institutions may take protective measures without having to wait until the reality and seriousness of those risks become fully apparent."

This finding is precisely what decision-making under risk is all about. The Court reasoned that the:

> "approach is borne out by Article 130r(1) of the EC Treaty, according to which Community policy on the environment is to pursue the objective inter alia of protecting human health. Article 130r(2) provides that that policy is to aim at a high level of protection and is to be based in particular on the principles that preventive action should be taken and that environmental protection requirements must be integrated into the definition and implementation of other Community policies."

In Case T-70/99, the President of the EU Court of First Instance referred to this judgment, stating that "the protection of public health should undoubtedly be given greater weight that economic considerations." Nonetheless, because of consistency with the Treaty of Union, case law and subsequent treaties, precautionary decisions must be based on sound analytical basis or else the assertion that "protection requirements must be integrated into the definition and implementation of other Community policies" cannot be met. We suggest that the weighting process is akin to portfolio management under risk: it is based on probabilistic weights assigned to each outcome.

A case involving Pfizer holds that the withdrawal of virginiamycin is a provisional measure subject to the Community Institutions' duty of reassessment. Lee and Stokes have commented on the EU actions on virginiamycin as follows:

> "However, although the parties to the case agreed that the framework of Directive 70/524 provides that Community institutions may adopt a measure on the basis of the precautionary principle, they disagreed on its interpretation. … Pfizer maintained that the Community institutions are prohibited from invoking precautionary measures unless and until they have undertaken a scientific assessment of the risks, and have shown that any such risks are probable. Pfizer contended that the Community institutions erred in their risk assessment. Although Pfizer accepted that the use of virginiamycin creates a 'hazard to human health', it argued that this is not enough to validate the withdrawal of authorisation on the grounds of the precautionary principle. Instead, Pfizer claims that a higher standard of proof should be imposed, and stated that '[i]t would be proven with the first dead man. It would be proven with the first infection, or with the first proof of colonization, or the first proof of transfer in a human.' The Court concluded that Pfizer's interpretation of the precautionary principle was incorrect. The Court noted that the application of the precautionary principle is acceptable in situations where there exists a risk to human health, even if it cannot be fully demonstrated, but it cannot be based on a purely hypothetical approach to risk. In the circumstances, it was held that the Community institutions did not surpass the limits of the discretion bestowed upon them by the Treaty when they concluded that there existed a proper scientific basis for a possible connection between the use of virginiamycin in feedingstuffs and the occurrence of streptogramin resistance in humans. Furthermore, the Court recognized the significance of a scientific study on live rats carried out by the Danish authorities and various reports from international, Community and national bodies, and claimed that it amounted to 'major fresh evidence' that virginiamycin created a risk to human health. The Court held that this additional information was undoubtedly based on the 'best scientific data available at international level.' The Court concluded that, overall, the Community institutions neither made manifest errors of risk assessment and risk management nor breached the precautionary principle."

Ironically, when virginiamycin, macrolides, and other animal antibiotics used to prevent animal illnessses and enhance performance were indeed withdrawn in several European countries, in keeping with this interpretation of the precautionary principle, bacterial illness rates in both chickens and humans increased dramatically, leading to greater need to treat both therapeutically and significant increases in human antibiotic resistance. The intended "precautionary" measure was followed by a substantial worsening in the problem it sought to prevent, although cause and effect have yet to be established (Phillips et al., 2004). These examples demonstrate that the EU procedure supports precautionary action tempered by scientific evidence and analyses but not always with the desired consequences. The EU regulatory approach primarily follows the relative form of the precautionary principle that, however, can benefit from the scientific, analytical framework.

United States

US law contains several variants of the precautionary principle in both environmental, heath, and safety law (Ricci and Gray, 1999; Ricci and Molton, 1981). An example is the language of the Toxic Substances Control Act, TSCA, which states that:

> "… If the Administrator finds that there is a reasonable basis to conclude that the manufacture,, processing, distribution in commerce, or disposal of a chemical substance or mixture, …, presents or will present an unreasonable risk of injury to health or the environment, the Administrator shall … protect adequately against such risk using the least burdensome requirements …"

As TSCA states, those least burdensome requirements are met by combining prudence (which allows for some level of reasonable risks) with the environmental, economic, and social costs of regulatory actions.[21] Administrative and legal processes that are designed to accomplish the tasks set forth by the legislature are lengthy and complex, with the potential for inaccurate, inefficient, and costly outcomes. The Comptroller General of the United States stated, in 1979, that:

> "Major constraints plague the Environmental Protection Agency's ability to set standards and issue regulations. The most important factor is the inconclusive scientific evidence on which it must often base decisions. Numerous court suits result."

This statement's importance and warning are particularly cogent and current for actions that fall under the principles of precaution because of the many legal and scientific difficulties. For example, in *Lead Industry Assoc., Inc. v. Environmental Protection Agency* (1980), after reviewing medical evidence of environmental exposure to lead and the resulting anemias, other adverse effects on the red blood cells, and neurological effects, the court found that the US EPA had acted reasonably in regulating lead, even when the uncertainty about the potential adverse health effects was large. Regarding this type of uncertainty, the US Supreme Court, in *Motor Vehicle Manufacturers' Assoc. v. State Farm Mutual Automobile Insurance Co.*,[22] held that:

> "Recognizing that policymaking in a complex society must account for uncertainty … does not imply that it is sufficient for an agency to merely recite the terms 'substantial uncertainty' as a justification for its actions (to revoke a safety standard). … The agency must explain the evidence that is available, and must offer 'a rational connection between facts found and the choice made.'"

Thus, the basis for developing actions under risk should normatively be guided by more than a mere assumption that is uncorroborated by factually relevant evidence or only a hypothetical (or conjectured) cause and effect relation. For example, the US Supreme Court in *Industrial Union Department v. American Petroleum Institute*, in the instance of issuing a permanent occupational standard limiting exposure in the workplace to airborne benzene, held that:

> "… the Secretary (of OSHA) is required to make a threshold finding that a place of employment is unsafe – in the sense that significant risks are present and can be eliminated or lessened by changes …"

In 1978, OSHA had used assumption, rather than empirical evidence or theoretical reasoning, to reduce the federal occupational standard for the 8-hour time-averaged airborne benzene concentration by a factor of ten (from the existing 10 ppm to 1 ppm). The OSH Act placed the burden of proof on OSHA to demonstrate that there was substantial evidence that it is more likely than not that long-term exposure to benzene presents a significant risk of material health impairment, rather than on industry. Although the legal issues inherent to this case involve the limits of delegation of powers from the legislature, this case gives guidance that is consistent with balancing the evidence of significant adverse impact – as oppose to some other degree of risk (risk is measured as an excess number of cancers over background) with imposing a permanent occupational health standard. In 1980, the US Supreme Court also held that:[23]

> "The reviewing court must take into consideration contradictory evidence … but the possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's findings from being supported by substantial evidence."

The Supreme Court indicated that the change in standard is not appropriate in the absence of adequate evidence. The benzene standard was changed again to 1 ppb in 1987, but only after OSHA had demonstrated sufficient epidemiological evidence and laboratory tests on animals.[24] This case demonstrates the need for an analytical system based on evidence that can incorporate new information, which might lead to establishing revised standards. The framework discussed later in this paper provides such an analytical system.

Broadly, an agency's rulemaking (standard setting) will be upheld by a court if: (i) there is a reasoned explanation of the basis of fact, (ii) substantial evidence supports the decision, (iii) other alternatives were explored and given reason for rejection, and (iv) the agency responded to public comments. The *arbitrary and capricious* standard of judicial review is also concerned with the reasonable set of alternatives that an agency should examine.[25] In this sense, the boundaries are relatively well-established, at least for the purpuse of precautionary choices under risk.[26] What does not appear to be well-established is the amount of deference that a court will give to an agency's rule-making.[27]

Regulatory analyses generally require the qualitative or quantitative determination of risks, costs, and benefits (including considering who benefits and who does not) to rank each of the options available to reach a regulatory standard, a discussion of the limitations of each, as well as allowing for public interveners.[28] American federal courts are generally deferential toward an agency's procedures and scientific judgment. As an example, when a court found that an agency did not comply with its own procedures, by not submitting its findings of causation to external peer review, that error did not invalidate the agency's rulemaking (Ricci and Gray, 1998). In *Chevron v. Natural Resources Defense Fund*, involving the interpretation of a section of the Clean Air Act, the US Supreme Court held that:

> "the Administrator's interpretation represents a reasonable accommodation of manifestly competing interests and is entitled to deference: the regulatory scheme is technical and complex, the agency considered matters in detailed and reasoned fashion, and the decision involves reconciling conflicting policies … When a challenge to an agency construction of a statutory provision , fairly conceptualized, really centers on the wisdom of the agency's policy, …, that challenge must fail."

For *contingent* actions to limit potentially severe or irreversible damages based on weak causation, our argument is that a minimally sufficient ammount of causal evidence should exist, before contingent evidence becomes available, suitably to determine the optimal choice from the set of reasonable alternatives. This argument is justified as follows. Some interpretations of precautionary principles favor correlative causal arguments, but add the strong requirement that subsequent scientific findings can be introduced either further to support the initial causal nexus or invalidate it. Thus, the necessary aspect of a causal argument for precautionary action under risk can be based on relatively weak evidence. In this sense, precautionary principles are congruent with legal causation, even when causation is more than merely correlative or the set of assumptions used is extended to include dose-response models that have that amount of theoretical and empirical foundations. Practically, even correlative arguments, the weakest form of quantitative causal reasoning, support the thesis that *non-linear (e.g., biphasic) dose-response models, given the state of the scientific evidence which we discuss later, should be included within the set of regulatory dose-response assumptions (also called defaults)*. It follows that stronger forms of causation (e.g., empirical or theoretical) reduce the need for contingencies: the sufficient condition on this argument is established at a later time when the contingency is removed.

Even when a statute (the Delaney Clause, 21 USC §376(b)(5)(B)) is, at least on its terms, unambiguous about the role of scientific evidence of causation, there can be litigation. The Delaney Clause states that:

> " … a color additive … shall be deemed unsafe … for any use … if , after test, which are appropriate … it is found by the secretary (of the FDA) to induce cancer in man or animal …,"

To illustrate, the FDA determined that exposure to Orange No. 17 and Red No. 19 caused excess cancers in laboratory animals. However, in a departure from the command of the Delaney Clause, the Administrator of the FDA, used the results from a risk assessment determining that the cancer risks would be trivial and thus allowed listing of these two color additives. In *Public Citizen v. Young*,[29] the court discounted the trivial risk argument (because it was not contemplated under the statute), focusing instead on literal meaning. It stated that judicial interpretations of statutory language are not limited by literal interpretations. However, because the court found that the scope of the Delaney Clause does not allow risk assessment, is limited to colorants of negligible or no nutritional value, and the intent of Congress (through the legislative history of the Delaney Clause) was explicit, it could not allow the FDA to use risk assessment to determine that those colorants were reasonably safe. In other words, even though the DC court understood that risks were very low and well within the range of acceptable individual risks, it could not let the FDA contravene the expressed intent of Congress. The US Supreme Court, in *Chevron, Inc. v. NRDC*,[30] had already stated that "[i]f the intent of Congress is clear, that is the end of the matter …." On the other hand, in *Chevron*, the Court held that when the clarity of intent is not present, the courts would defer to the way an agency interprets a statute.

The process of setting federal US environmental standards illustrates how the US EPA deals with partial information and cost-benefit analysis. In 1982, the US EPA reviewed the particulate matter (PM_{10}) standard; however, in 1992, the EPA did not again review the PM_{10} standard, as commanded by the Clean Air Act. The American Lung Association then sued the agency to force review, and to make sure that the air pollution standards for particulate matter would also include $PM_{2.5}$.[31] The court then ordered the EPA to review the scientific evidence for a new standard (Faigman, 2000). However, the peer review of the literature, the use of that literature, and a US EPA-funded study mandated by Congress and done by the Clean Air Scientific Advisory Committee, CASAC, were controversial. Nonetheless, although there was general agreement of the need to set a standard for $PM_{2.5}$, there was division among the members of CASAC about the adverse effect of different exposures on the lung. In the end, CASAC did not endorse the proposed EPA's $PM_{2.5}$ standard because it found that the science was too weak to lend support for the specific levels chosen by the EPA. The reasons were weak empirical causation, uncertainty and the high cost of meeting the new standards. This is a useful example for future review and potential revision as more information and data become available. It further illustrates the need for a framework with the formal flexibly to accom-

modate such new information.

The issue of considering regulatory costs became legally controversial in setting primary standards for criteria air pollutants (which include particulate matter). The US Supreme Court affirmed that, under Section 109 of the CAA (Amended)[32], federal standards (the National Ambient Air Quality Standards, NAAQS, section of the CAA) for particulate matter and tropospheric ozone must be set without consideration of costs and benefits. This case, *Whitman, Admin. of EPA, et al., v. American Trucking Associations, Inc., et al.*,[33] addresses four issues. Two of these are important to understanding the setting of ambient environmental standards to protect the public health with an adequate margin of safety. This standard protects susceptible populations, not just the public. The Court held that the US EPA cannot arbitrarily construe statutory language to nullify provisions (contained in a statute) meant to limit that agency's discretion. It also held that section 109(b) of the CAA does not permit the Administrator to consider implementation costs in setting NAAQS because that section of the CAA does not contain language regarding such consideration.[34] However, the Court also held that the states of the Union could base their risk management actions by accounting for costs and benefits of any action that they consider.

As discussed, the courts will review an agency's regulatory action on the basis of the "arbitrary, capricious, and abuse of discretion" standard or will determine if an agency made "a clear error in judgment." This judicial standard is more intricate than the other standards we discuss because it involves many diverse considerations, including public policy. These considerations range from whether a court should review the substance of an agency's action or limit itself to the procedural aspects of that action. Part of the issue has to do with the extent and scope of delegated (legislative and executive) powers to the an agency, in term of how it has used science to support its regulatory action. More specifically, a court will assess if and how the factors that have lead to the action are relevant to that action, and assess if that agency has made a "clear error in judgment." Although prior Congressional guidance is critical, if the agency accounted for the factors that the statute under which the agency operates requires, then the agency did not act arbitrarily.

TOWARDS A CONSTRUCTIVE FRAMEWORK FOR IMPLEMENTING PRECAUTIONARY PRINCIPLES

In this section, the legal and regulatory considerations of the previous section are placed in the context of practical implementation of precautionary maxims, regardless of jurisdiction. We first outline a scientific, casual approach that is invariant to either the absolute or relative form of precautionary principles.

The EU (2001) states that the appropriate response under the Precautionary Principle results from political decisions, which depend on the risk level that is "acceptable" to those in society on whom the hazard can potentially fall. This is the equitable aspect of the social calculus. The EU Communication (2001) states that precautionary:

> "measures, although provisional, shall be maintained as long as the scientific data remain incomplete, imprecise or inconclusive and as long as the risk is considered too high to be imposed on society. Maintenance of the measures depends on the development of scientific knowledge, in the light of which they should be reevaluated. This means that scientific research shall be continued with a view to obtaining more complete data. Measures based on the precautionary principle shall be reexamined and if necessary modified depending on the results of the scientific research and the follow up of their impact."

Thus, the implementation of the EU's precautionary principle is contingent and must thus account for future information and knowledge. The methods to deal with these situations, which fall within our *Risky A* and *Risky B* dichotomy, now exist. These, at least in part, are discussed by Van der Haegen (EU, 2001) who comments that the:

> "approach to the analysis of risk which comprises three elements: risk assessment, risk management, risk communication. The precautionary principle is above all a risk management tool. Decision-makers need to be aware of the degree of uncertainty attached to the results of the evaluation of the available scientific information. Judging what is an "acceptable" level of risk for society is an eminently political responsibility. Indeed, if something goes wrong those in charge of the risk management are accountable."

Scientifically, normatively, and legally, management actions must account for potentially beneficial outcomes, as well as potentially hazardous ones. Contingent decisions are designed to be resilient to new information and knowledge, and thus should account for both outcomes. To be truly protective, it is myopic to assume as a default that all exposures, other than zero exposure, are detrimental if beneficial, or even neutral effects can occur at very low doses. This symmetric approach to precaution is clearly consistent with seeking additional scientific information and prudent decision-making under risk. Causal reasoning uses deduction, induction, and abduction to discover causal knowledge from empirical knowledge, leading to working hypothesis of causation. Induction and abduction are prominent because they link scientific evidence to the causal conclusion in the most natural, explanatory way, while deduction resides in known physical laws. Because of the potential costs of risky decisions to society, a formal causal structure should accompany social decision-making to justify choices. This, however, is not equivalent to asserting that political and other values have no place in social decisions; quite the opposite. Rather, formal justifications are an important societal asset, and are consistent with qualitative and quantitative measures of risk. To do otherwise conflicts with a number of heuristics andbi ases (Kahneman, Slovic, and Tversky, 1981; Howson

and Urbach, 1993) that plague informal reasoning.

In the context of precautionary principles, equivalent to contingent decision-making under either risk or uncertainty with retraction, we suggest that the principal issue is not whether courts should be strict constructionists, deference has gone too far, or whether other legal doctrinal issues are problematic for the just and fair implementation of precautionary principles. Rather, the issue is that scientific evidence and causation are uncertain or unknown, thus requiring assessments that are consistent with the art and science of decision-making. We propose the following axioms as a basis for precautionary decision-making under risk:

Principle I: Risk-cost-benefit balancing is *sine qua non* in societal decision-making. The rationale is that society must allocate scarce resources and that the balancing of risks, costs and benefits leading to an optimal (or sub-optimal) choice always occurs, either implicitly or explicitly.
Principle II: Prospective decision making under risk is probabilistic. The rationale is that precautionary principles deal with future adverse, severe or irreversible potential outcomes.
Principle III: Prospective decision-making under uncertainty uses measures of uncertainty that can include probabilities. The rationale is that decision-making under uncertainty can disallow probabilistic measures tout court.
Principle IV: Causation under risk is probabilistic. The rationale is that probable cause adverse effect relations can be falsified or updated by new knowledge.
Principle V: Decisions justified by tolerable or acceptable risk criteria (such as de minimis or zero risk) are incomplete. The rationale is that benefits and costs must be considered as well (Principle I) and that future information about them may supersede previous judgments about what is "acceptable".

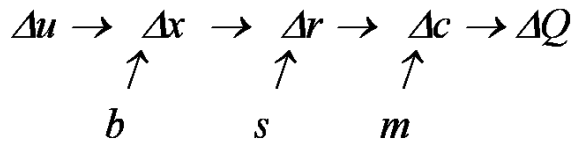
Sunstein (2003) writes that "the precautionary principle often seems appealing because of loss aversion … (because) … people dislike losses far more than they like corresponding gains." He then suggests that, "in a situation of uncertainty, when existing knowledge does not permit regulators to assign probabilities to outcomes, it is standard to follow the minimax principle: to choose the policy with the best worst case outcome." However, such rules, which ignore probabilities, are inconsistent with widely adopted axioms of "rational" choice that justify subjective expected utility (SEU) as a basis for decision-making under uncertainty (and risk). Regardless of whether a public decision-maker should uses a version of expected utility or other criteria to define and make societally optimal choices, causation is *sine qua non*, legally and scientifically.

What is needed is an analytical basis for assessing risks while accounting for causation in a legally and scientifically defensible way. Risk assessment is a necessary element of social, economic, and political analysis, which regulatory agencies routinely perform. Specifically, the analytical framework, the fundamental causal network FCN, that we develop next is consistent with determinations made legally and scientifically through the range of tests we have discussed.

Fundamental Causal Diagram, FCD

Legally, theoretically, and pragmatically, the application of any form of the precautionary principle must reflect the fundamental causal network, FCN, Figure 1

Figure 1, Fundamental Causal Network



In this network:

Δu = risk management act to be evaluated (e.g., a change in use of a product or exposure),
Δx = change in exposure, if act Δu is taken,
Δr = change in illnesses (the "response" in dose-response models or exposure-response models) caused by Δx,
Δc = change in adverse health consequences caused by Δr,
ΔQ = change in a summary measure of risk (e.g., change in expected quality-adjusted life-years, QALYs, lost per capita-year, when this is an appropriate measure) caused by Δc.

This sequence of changes in response to Δu may be modified by other variables, such as:

b = individual behaviors or other factors that affect or modify exposures, given Δu,
s = individual susceptibility and/or other covariates that affect or modify the dose-response relation. Inter-individual variability in dose-response relations can be modeled in terms of differences in s; in this case, s may be a latent variable or contain latent or unobserved components, as in finite mixture distribution models.
m = individual medical treatment and/or other factors that affect or modify the illness-consequence relation.

Thus, a scientific structure based on the FCN can aid decision-makers and stakeholders because it is (piece-wise) consistent with biphasic modes of action, if these are known. It should consist of a framework that allows consistent evaluations under risk, updating when additional information becomes available, thus reducing legal ambiguity. The characterization of risk can be performed for a proposed risk management intervention u, once the exposure modeling and dose-response modeling steps are complete, by "marginalizing out" the remaining variables, i.e., summing (or integrating, for continuous random variables) over their possible values. For example, the composition of the relations $Pr(\Delta x \mid \Delta u)$, $Pr(\Delta r \mid \Delta x)$ and $Pr(\Delta c \mid \Delta \rho)$ yields the probability density (and thus the expected value) of the human health consequence (c):

$$Pr(\Delta c \mid \Delta u) = \Sigma_{\Delta r} Pr(\Delta c \mid \Delta r) Pr(\Delta r \mid \Delta u) = \Sigma_{\Delta r} \{Pr(\Delta c \mid \Delta r)[\Sigma_{\Delta x} Pr(\Delta r \mid \Delta x) Pr(\Delta r \mid \Delta u)]\}$$

This collapses the entire causal chain ($\Delta u \rightarrow \Delta x \rightarrow \Delta r \rightarrow \Delta c$) to a single but equivalent risk characterization link ($\Delta u \rightarrow \Delta c$) = $Pr(\Delta c \mid \Delta u)$ and relates risk management actions to their probable health consequences. More generally, if the main sequence ($\Delta u \rightarrow \Delta x \rightarrow \Delta r \rightarrow \Delta c$) is embedded in a larger directed acyclic graph (DAG) model with the conditional probability distribution of the value of each node (representing a variable in the model) being determined by the values of the variables that point into it, then the conditional probability distribution for $\Delta c \mid \Delta u$ can be calculated via computational methods for exact inference in Bayesian networks and causal graphs (Pearl, 2000). A simpler approximate method is Monte Carlo simulation, if no Bayesian inference is required. Then, commercially available software, such as @RISK™, CrystalBall™ and Analytica™, can be used to sample values from the probability distributions of input nodes (nodes with only outward-directed arrows) and propagate them forward through deterministic formulas and conditional probability look-up tables stored at other nodes, to create approximate distributions for the values of output nodes (those with only inward-directed arrows). However, if Bayesian inference is used to condition on data, while propagating input distributions to obtain output distributions, then Bayesian Net Toolbox or WinBUGS can perform computationally intensive stochastic sampling (typically, using algorithms such as Gibbs sampling and other Markov Chain Monte Carlo (MCMC) methods) for accurate, but still approximate, inference using DAGs. In either instance, a risk assessment model is fully specified using the FCN by setting either its node formulas or conditional probability tables at each node. These determine the probability distribution of values for each node conditioned on its inputs. Effective computational inference algorithms and software for quantifying $E(\Delta c \mid \Delta u)$ and $Pr(\Delta c \mid \Delta u)$, while conditioning on any relevant data (for individual cases), exist. Therefore, most applied risk assessment effort can focus on using available data to quantify the component causal relations for the nodes, $Pr(\Delta x \mid \Delta u, b)$, $Pr(\Delta r \mid \Delta x, s)$, and $Pr(\Delta c \mid \Delta r, m)$: the exposure, dose-response, and health consequence models. These components can then be composed jointly to compose the causal path from actions to health consequences and to complete the risk assessment by computing $E(\Delta c \mid \Delta u)$ or $Pr(\Delta c \mid \Delta u)$.

QUALITATIVE v. QUANTITATIVE ANALYSIS OF RISKS IN THE CONTEXT OF AN INSTRUMENTAL PRECAUTIONARY PRINCIPLE

Achieving a convergence between fundamental legal principles in a socially efficient way, while dealing with uncertainty and variability, suggests using a unified formal framework that can enhance the harmonization of laws that apply a precautionary principle. As we have discussed, legal analyses are fundamentally qualitative. A number of international jurisdictions have developed qualitative risk assessment methods to rank hazardous situations, rather than relying on quantitative risk analysis. Quantitative analysis can help identify the limitations of what any risk rating or risk-ranking system – qualitative or quantitative – can achieve. For example, suppose that a rating system is to be used to compare two different options, A and B, to determine which should be ranked higher, e.g., in a priority order for regulatory concern or intervention. If the overall rating of risk is to be based on component ratings of several risk components or factors, as in all of the above examples, then how should the overall risk rating of alternatives A and B depend on the component ratings? Some plausible properties might be:

Axiomatic Properties for Aggregating Component Scores into Final Risk Scores

1. Which of alternatives A and B is rated higher in the overall risk rating should depend only on their component ratings. Thus, the components used to rate risk should be sufficient to do the job: together, they determine whether A is assigned a higher, equal, or lower rating than B.
2. Which of A and B is rated higher on overall risk depends on each of their component ratings. Specifically, if A and B are identical in all respects except that A rates higher or worse than B on one factor (e.g., exposure), then B should not be rated higher than A in the overall risk rating. This property should hold for all the risk components: none of them is irrelevant.
3. If A rates higher (or lower) than B on every component rating, then B should be rated no higher (or lower) than A in the overall risk rating.
4. Risk ratings of A and B should be based only on their own data, i.e., whether A is rated higher or lower than B should not depend on what other alternatives (other than A and B) are also being rated, if any.
5. If one or more component ratings are zero (e.g., for exposure potential or for human health impact potential of exposure), then the overall risk rating should be zero (or "Negligible" in systems with that category).
6. If the rating for a component is uncertain (e.g., if it has a 0.2 probability of being "L", 0.5 probability of being "M", and 0.3 probability of being "H"), then the single "equivalent" rating assigned to that component (i.e., H, M, or L after considering its uncertainty) should not depend on the ratings assigned to the other components.

Such logical relations among the ratings of components and the overall risk rating put strong constraints on the choice and use of possible rating systems. For example, if quantitative ratings are used, then conditions such as 5 and 6 imply that the aggregation formula used to combine component ratings into an overall risk rating must be multiplicative, i.e., the overall risk rating is proportional to a product of its component ratings (Miyamoto et al., 1998). Such multiplicative aggregation of quantitative ratings satisfies properties 1-4.

On the other hand, if only qualitative rankings are used for the components, then it turns out that there is no qualitative ranking system that can assign coherent overall risk rankings (meaning complete, transitive rank-orderings with ties allowed) based on arbitrary component rank-orderings in such a way that principles 1-4 are satisfied (Arrow, 1963). Similar limitations hold for aggregating fuzzy ratings of linguistic labels or scales (e.g., H (High), M (Medium), L (Low), and N (Negligible), depending on how they are formalized. In other words, qualitative component ratings alone, without further mathematical operation (e.g., multiplication) may not contain enough information to be coherently aggregated into an overall qualitative risk rating that is related to them normatively Another concern is that a risk rating system with only a few possible outcome categories may not produce enough information to assist making a decision if it is not inclusive enough to support effective decision-making. For example, as developed in Australia, a 3*4 matrix assigning a label of H, M, L, or N to each of three components (Hazard, Exposure, and Impact) can provide only a small amount of information (technically, at most six bits of information, equal to the information content of six tosses of a fair coin) to guide decision-makers, Table 2.

Of the much larger quantities of potentially useful and relevant information collected and entered into such a rating scheme (several hundred bits at a conservative estimate), almost all is lost in aggregation during the rating process. This can be a regrettable loss, if it affects decision-making on behalf of society. The small fraction that remains (6 bits in this case, or even less if the probabilities of the 12 cells are not all equal) may be insufficient for effective decision-making, which typically requires at least enough information to discriminate among alternatives that have very differently preferred outcomes. The minimum amount of complexity and information required for a classification system (including a risk rating system) to make few errors can be rigorously analyzed via techniques from information theory and statistical learning theory. A key insight from such formal analysis is that a classification system that lacks enough complexity to discriminate well among essentially different situations may lead to poor decisions, i.e., ratings with high error rates and high expected losses from decision errors.

Comparing Risk Management Recommendations from Qualitative and Quantitative Approaches

If we consider the administration of antibiotics to poultry as an example, the main risk management recommendations emerging from qualitative risk classification approaches are to "strictly limit" animal uses of antibiotics classified as "critically important" in human medicine. In general, such a qualitative mapping from risk components to action categories belongs to a broad class of "if-then" risk management rules mapping situa-

Table 2, Qualitative Risk Assessment Framework from Australia (each factor is rated H, L, M, or N)

Factor	Definition
Hazard = source of risk	Antibiotic resistant microorganisms or their resistance plasmids (that have the potential to transfer to humans) within an animal species, arising from the use of an antibiotic in an animal species
Exposure	Amount and frequency of exposure of susceptible humans to antibiotic-resistant microorganisms (or their plasmids) from animal sources
Impact	The evaluation of infections (caused by antibiotic-resistant pathogens of animal origin) in susceptible humans. Considers: a) Perceived or known clinical importance of the class of antibiotics to humans; b) Dose-response assessment of relationship between frequency and magnitude of exposure of humans (dose) to antibiotic – resistant food-borne microorganisms and severity and/or frequency of the impact (response); including an estimate of the critical threshold of exposure required to cause infection in susceptible humans. c) Antibiotic-resistant disease severity, morbidity, mortality. d) Expected numbers of infections and deaths. e) The impact on human health and quality of life including the range of the susceptible humans expected to be affected. Probability of antibiotic-resistant infection development in susceptible humans (N, L, M, H)

Adapted from Australia National Registration Authority Veterinary Requirements Series, Part 10
http://www.apvma.gov.au/guidelines/vetguideline10.pdf.

tions to actions. Other examples include: Ban or restrict an agent if its risk is deemed "unacceptable", or if it is deemed "precautionary" to do so, or if a resistance threshold "trigger level" is passed in surveillance data, or if the drug is classified as "critically important" in human medicine, or if it is classified as "not essential" for animal use, and so forth. Logically, such if-then rules can be incompatible with rational (consequence-driven) decision-making in some applications, as they are triggered by recognition of a situation (the "if" part) rather than by explicit assessment of the probable consequences of actions (the "then" part) and selection of actions to make desired consequences more probable – the *sine qua non* of traditional rational decision-making.

Rule-based risk management decision procedures that do not explicitly identify or optimize the quantitative human health impacts of recommended interventions and classifications can trigger pre-specified actions (e.g., interventions to withdraw or restrict a source of exposure) that unintentionally do more harm than good, creating unintended adverse consequences for human health. Rational risk management requires comparing the probable consequences of alternative risk management actions and then choosing the available action with the most desirable probability distribution of consequences. Substituting "importance" in human medicine, or other non-consequential criteria, for actual human health consequences as a guide to risk management decision-making, may lead to recommended actions that create far more harm to human health than they prevent. Methodologically, no small number of qualitative labels for risk and its components can suffice to make effective risk management decisions. We formalize this as follows:

Axiomatic Approach. A minimal requirement for effective decision-making might be that actions with Risk (act) > Risk (status quo), i.e., those that do more harm than good to human health, should not be recommended. (A stronger requirement would be that no act should be selected for implementation if an alternative act with preferred consequences is available.) To decide whether [Risk (act) – Risk (status quo)] > 0, it is necessary to assess both the human health risks and benefits of the act well enough to decide whether their difference exceeds (status quo). The ability systematically to compare such differences implies that risks and benefits can be represented numerically (on a "difference scale" that is unique up to choice of unit), under well-known conditions [the "axioms of difference measurement" in measurement theory (Luce and Suppes, 2001)] for coherent qualitative ranking of differences. Under these conditions, ability to compare differences implies that risks and benefits can be represented quantitatively.

*Error Probability Approach. Su*ppose that we want to identify acts for which BENEFIT – RISK > 0, with high probability. For simplicity, suppose that RISK and BENEFIT are modeled as independently uniformly distributed random variables (with bounded ranges) for the set of alternative risk management acts being considered. Each act corresponds to a pair of (RISK, BENEFIT) attribute values drawn uniformly from the entire rectangle of possible values. If we use N qualitative labels to classify the RISK and BENEFIT of each act, corresponding to partitioning their continuous ranges of possible values into N contiguous intervals (such as H, M, L), then the error rate in classifying acts with BENEFIT – RISK > 0 will be 0.5/N (since a rectangular grid of N*N cells will separate cases with BENEFIT – RISK > 0 perfectly except along the diagonal of N cells with the same rating level on each attribute, where the error rate is 50%.) To identify "good" actions with an error rate of no more than 5% would require at least N = 10 levels. (On the other hand, with N levels, one has a (1–1/N) probability that an act will be correctly classified with certainty.) Similar analyses can be extended to more factors and more complicated decision boundaries, e.g., to quantify the error probability as a function of N when the goal is to determine whether the product of exposure, illness-per-exposure, and consequence-per-illness, factors exceeds a certain level. In general, using too few qualitative labels for the factors leads to excessive error rates.

Information Theoretic Approach. Even without formal axioms or quantitative analysis of decision error probabilities, it is perhaps obvious that determining whether the net human health benefits of an act achieves at least a certain target threshold (e.g., the net benefit of the status quo or the best act identified so far) requires at least enough information to determine whether any of the causal factors is zero.

Often, risk can be expressed as a product of several factors or fractions, such as the fraction of ingested servings that carry infectious doses of a pathogen; the fraction of these servings that cause illness; the fraction of the illness cases that receive treatment, and so forth. But, these fractions are all logically independent: i.e., whether one is zero is not determined or constrained by whether others are. Hence, there is no way to represent the answers to which ones are non-zero by any set of three-level (e.g., H, M, L) or four-level (e.g., H, M, L, N) ratings of three components, as there are only $3^3 = 27$ possible configurations of qualitative rating (or $4^3 = 64$ configurations when a four-level rating is used) compared to $2^8 = 256$ configurations of yes-no answers to whether each of 8 factors is non-zero. Similarly, there is no way to use a 3-attribute, 3-level rating system to show whether each of at least 6 factors is large enough so that their product can exceed a specified level. Even without further refinements, it is clear that any such qualitative rating system, regardless of the exact design and interpretation of its component attributes and rating scores, will in general be too limited to represent the information needed to decide whether there are positive net benefits from a proposed action, let alone to decide, which action is best or whether a given action is worth undertaking. More generally, any qualitative rating system can be interpreted as a classifier (producing qualitative labels as output) and evaluated by comparing the average bits of information required to make a correct risk management decision with high probability (using information theory bounds for classifiers) to the number of bits of information actually provided by the rating system. The

calculations illustrate the more general point that insufficiently informative ratings cannot support decision-making with low error rates.

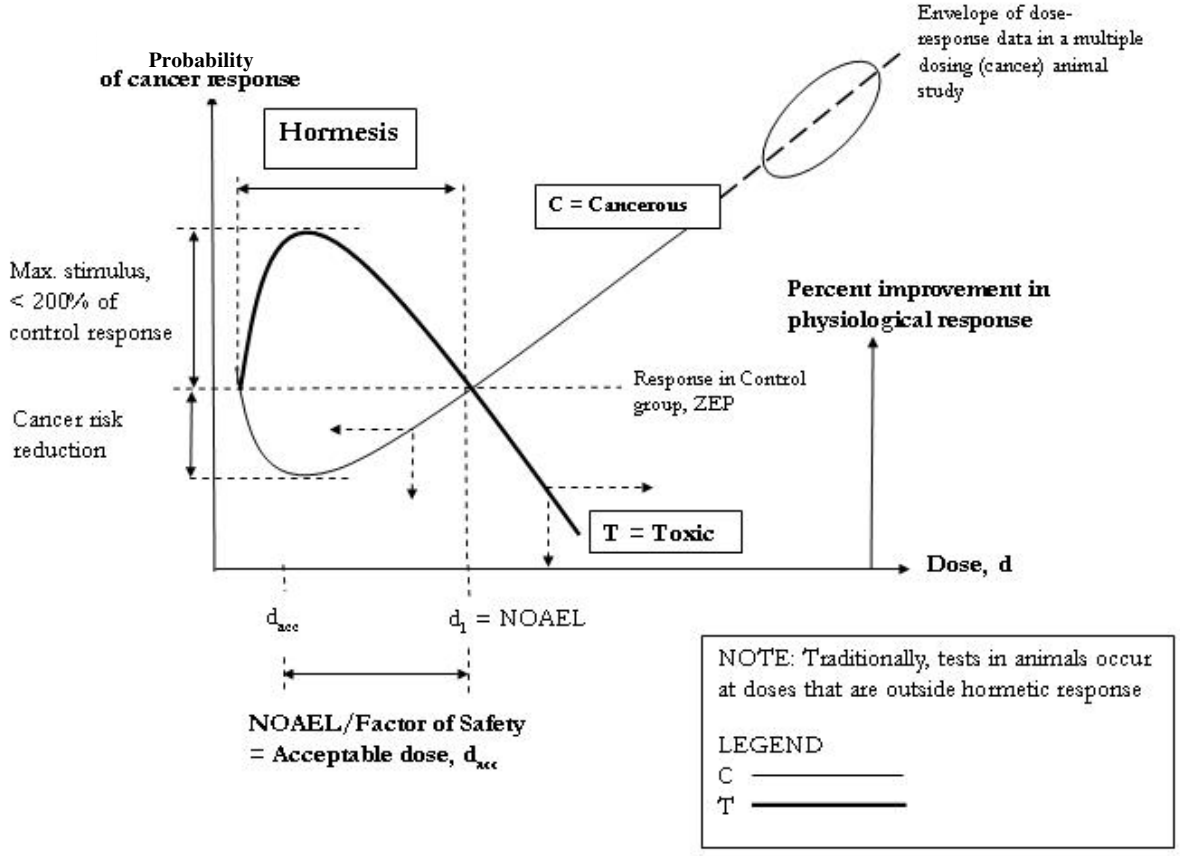
In summary, qualitative rating systems with too few components and rating categories cannot support effective risk management decision-making that produces preferred consequences with high probability. Including enough information to allow changes in human health impacts produced by alternative risk management interventions to be coherently ranked may require quantitative rating scales. However, this may be desirable because a relatively simple quantitative risk rating system based on multiplying factors (or place bounds on them, when there is uncertainty) and then summing the products over different combinations of conditions can quickly provide enough quantitative information to identify the best among competing decision options, even without resolving all relevant scientific uncertainties. Thus, a scientific structure based on the FCN can aid decision-makers and stakeholders. It should consist of a framework that allows consistent evaluations under uncertainty, updating when additional information becomes available, reducing legal ambiguity. The characterization of risk can be performed for a proposed risk management intervention Δu, once the exposure modeling and dose-response modeling steps are complete, by "marginalizing out" the remaining variables, i.e., summing (or integrating, for continuous random variables) over their possible values.

HORMESIS AS A DEFAULT IN RISK-BASED HEALTH DECISIONS

The biphasic response consists of a toxic effect followed by a correction, induced by homeostasis (Stebbing, 1982). We show the prototypical biphasic dose-response for carcinogenic and other toxic outcomes in Figure 2. The NOAEL is defined (Calabrese and Baldwin, 2001) "as the highest dose with a response not statistically different from the control, with respect to the adverse effect in studies where hypothesis testing was performed."

A hormetic (or biphasic) dose-response is non-monotonic, unlike the threshold models and the linearized multistage cancer risk model. The fact that we can often observe a j- or u-shaped dose-response has particular relevance to the precautionary actions because a non-threshold model is more protective than using a regulatory agency default dose-response assumptions. Hormesis, measured at exposure and doses below those causing chronic effects, is generalizable; therefore accounting for it in risk-cost-benefit analyses is essential to precautionary and societally optimal regulations. The key finding of relevance to precautionary actions is that (Calabrese and Baldwin, 2003) "hormetic response is more common than the threshold model in toxicology." Calabrese and Baldwin (2003) have studied this issue and found that hormetic mechanisms are more prevalent than threshold mechanisms. Their key

Figure 2, Hormetic, Non-linear Dose-Response Model for Cancer and Non-cancer Endpoints



conclusion, based on an analysis of approximately 1,800 doses below the NOAEL from more than 650 dose-response studies, is that:

> "While the threshold model predicts a 1:1 ratio of responses 'greater than' to 'less than' the control response (i.e., a random distribution), a 2.5:1 ratio (i.e., 1171:464) was observed, reflecting 31% more response above the control value than expected (p-value < 0.0001). The mean response (calculated as % control response) of doses below the NOAEL was 115% ± 1.5 standard error of the mean (SEM)."

Moreover, "residual toxicity," in which a toxic effect may persist in the neighborhood of the NOAEL dose, can reduce the findings even more hormetic behaviors. Calabrese and Baldwin (2003) find that approximately:

> "70% of the vertebrate toxicology studies assessed here had NOAELs less than the control, it suggests the possibility of residual toxicity in a … percentage of such dose-response relationships, a factor that could significantly underestimate the frequency of hormesis in vertebrate toxicological literature."

Calabrese and Baldwin (2001, 2003) have based their assessments of hormetic mechanisms on a selection of past studies, and have developed and used a ranking based on a protocol in which they account for the completeness and statistical quality of the studies used. Their protocol also accounts for false negative and false negative probabilities of error.

Some (e.g., Chapman, 2001) have suggested that hormetic dose-response should be used for detailed risk assessments. We think that this option is unnecessary because there is sufficient evidence (Calabrese and Baldwin, 2001, 2003) that a hormetic dose-response can be as legally valid as the linear, non-threshold alternatives, under the rules of evidence law. For the US, the key cases are: *Frye*[35] and *Daubert*[36], which deal with the admissibility of scientific evidence. In *Joiner*[37] the Court held that the Court of Appeals (for the 11th Circuit) did not sufficiently give deference to the trial court evidentiary rulings because it (the court of appeals) interpreted the law of evidence too stringently: in doing so, it abused its discretion. The standard of judicial review of these trial courts' opinions by courts of appeal, generally is the "abuse of discretion" test[38]. At least in the US, trial courts are the "gatekeepers": scientific evidence must pass that gate, and thus become admissible, before it can be used in a trial. The trial judge makes the finding of what is, and is not, admissible to the actual trial (Ricci and Gray, 1998, 1999).

VALUE OF INFORMATION (VOI) VS. PRECAUTIONARY APPROACHES

Contingent decisions under precaution, particularly if the stakes for society are large, should account for the potential effects on the initial probabilities of new information – and use these effects to decide whether to acquire costly information. More specifically, not only is the cost of new information important, but also the notion that potential economic costs and benefits should be accounted for, before implementing a decision from the set of potential decisions available to the decision-maker (Clement, 1996). The relevant framework, consistent with Bayesian decisions, is based on the value of information (VOI) (Yokota and Thompson, 2004). To illustrate the VOI framework, we use a case study that assesses the management dilemma posed by the potential for infection in the US from imported Canadian cattle. The detection of two bovine spongiforme encephalopathy, BSE, cases from Alberta in less than a year in 2003 raises the question of the actual magnitude of the true prevalence of BSE in Canadian cattle, and of its impact on the US. The statistical inference problem is complicated by the fact that a single cow in Washington state was not detected as part of Canada's routine sampling program, and the probability that such cattle will be detected once they have been imported into the US is not known. From a risk management perspective, the key question is what actions, if any, the US should take now in light of uncertainty about the true prevalence rate of BSE among Canadian cattle now, and in the future. This decision problem is made more challenging by scientific uncertainties regarding BSE sources, reservoirs, and dynamics, such as:

- Roles of horizontal and vertical transmission (if any) within herds
- Existing and potential BSE reservoirs in Canada and the US
- Transmission dynamics within and between differ ent reservoirs
- Interindividual differences in susceptibility among cattle of the same age
- Distribution of infectivity and differences in virulence among new BSE cases
- Distribution of latency period to clinical finding; possibility of subclinical cases
- Potential for clustering of rare events within geographic areas, processing plants, affected populations etc.
- Error and compliance rates (such as mislabeling, etc.) in Canada and the US
- Possible heterogeneity of the basic reproductive rate for BSE in different geographic areas or for different strains of BSE, different types of cattle, etc.
- Detection probabilities per case, given the target and sampling schemes used and the tissues sampled

With so many unknowns, predictive modeling is uncertain. Actual data on observed cases of BSE can therefore be valuable for improving estimates of true BSE prevalence. However, the two BSE cases from Alberta detected in 2003 support alternative interpretations, ranging from the first beginnings of a wave of BSE cases to the last remnants of a problem from the 1980s and 1990s that has already been fixed and that, by

chance, escaped detection until 2003. The data do not reveal a unique correct interpretation (Cox, 2002). This dilemma is precisely what the practitioners of risk management face when considering actions to be taken under any of the forms of the precautionary principle This dilemma is as follows. On the one hand, experience since 2003 has shown that discovery of BSE cases in the US can dramatically reduce US beef exports, even if the infected animals originated in Canada. If the true prevalence of BSE in Canadian cattle shipped to the US were known to be as high as the current sample-based mean of about *6.0E-6*, then continued prevention of cattle imports from Canada might be expected. On the other hand, if the prevalence of BSE in Canadian cattle were known to be *0*, then the advantages of resumed trade could be gained by allowing unrestricted imports, without incurring the risk of additional BSE cases. Given the high economic stakes and the uncertainties about the prevalence of BSE in Canadian cattle (and, for that matter, US cattle), it has been difficult to determine what policies would best promote US and international interests. The managerial options range from maintaining the status quo (e.g., preserving current import restrictions and testing programs) to tightening or loosening current import policies to gathering more information first – for example, by tracking all imported cattle and testing all Canadian cattle in the US – and then using this information and the results of future sampling to decide when and whether to change import restrictions. To discover which of these (or other) options is most desirable, it is necessary to compare the conditional probability distributions of gains and losses for each option.

The problem can be modeled formally as follows (Cox et al., 2004). First, an initial ("Stage 1") decision must be made either to track Canadian cattle in the US ("Track CA imports") or not to track them ("Do not track CA imports"). If the Stage 1 decision is "Track CA imports", then any of the following informative events may be observed over the following time period (e.g., 1 year):

- No new BSE cases detected
- BSE case of Canadian origin detected in US
- BSE case of US origin detected in US
- BSE case of Canadian origin detected in Canada

If the Stage 1 decision is "Don't track CA imports", then the four possible observations for the next period are aggregated to only the following three:

- No new BSE cases detected
- New BSE case detected in Canada
- New BSE case detected in US

After the Stage 1 decision, and given updated information about any new BSE cases, a subsequent ("Stage 2") decision must be made about whether to sell and process healthy-appearing cattle without first requiring them to be tested for BSE ("No required test") vs. requiring all US cattle to be tested for BSE before being sold or processed ("Test all") vs. requiring only all Canadian cattle in the US to be tested for BSE before being sold or processed ("Require testing for CA cattle only".) The latter option is available only if the Stage 1 decision was "Track CA imports." In addition to any required testing, some cattle will continue to be sampled and tested according to a USDA test program, and this is not affected by the Stage 1 and Stage 2 decisions. The Stage 2 decision presumably will be made to obtain the most desirable outcome possible, given the information available then. For example, if a new BSE case is detected in the US and its origin cannot be ascertained, then the Stage 2 decision might be "Test all" US cattle at slaughter, to reduce export and domestic consumption losses (if the economic benefits outweigh the costs of testing); while if the origin of the case is known to be Canadian and the Stage 1 decision was to "Track CA imports", then the best Stage 2 decision might be "Require testing for CA cattle only".

After Stage 1 and Stage 2 decisions have been made and the future information has been obtained, it becomes possible to evaluate how much beef consumption, if any, has been lost in export and domestic markets due to BSE cases and risk management responses, and how much the Stage 1 and Stage 2 decisions cost to implement. A goal for rational risk management decision-making today is to anticipate how current decisions change probable future total costs (i.e., the sum of implementation costs and costs from lost domestic and export sales) as they will eventually be assessed in hindsight. Each Stage 1 decision, in conjunction with optimized Stage 2 decisions given future information, determines a probability distribution for total cost. Rational risk management requires making the choice today that induces the most desirable probability distribution for total costs, as they eventually will be evaluated in the future.

The decision-analytic/VOI approach to risk management proceeds through the following steps:

1. Identify a set of alternative decision rules or options to be compared. A decision rule specifies the actions to be taken at each time (e.g., whether to track Canadian cattle, whether to test all US cattle or all Canadian imports or just continue surveillance sampling), given the information available then. It may be thought of as a plan that specifies what to do under different contingencies.
2. Identify the consequences of concern, which the actions may affect. (These may include loss of domestic and export sales if a BSE case is found – with the loss to the US being far larger if its origin is not known than if it is known to be Canadian).
3. Identify the probabilities of different consequences, for each decision rule. This typically requires considering different scenarios or assumption sets describing alternative ways in which current uncertainties might be resolved. These are

also called "states of nature". Often, there is no objective, uniquely correct way to determine the prior probabilities of alternative scenarios. Then, conservative assumptions (tending to favor the status quo) and sensitivity analyses (in which various prior probabilities of scenarios are assumed) may be used to determine how robust the conclusions and decision recommendations from the analysis are to variations in scenario probabilities.

4. Identify the optimal decision rule, defined as the one with the most desirable probability distribution of consequences, given current information and assuming that future actions (including information-collecting actions) will be made optimally given future information.
5. Identify and recommend the optimal current action, as determined by the optimal decision rule.

Given that the very limited available evidence favors the hypothesis that Canadian BSE prevalence is higher than US BSE prevalence and that these scenarios imply relatively high information values for tracking Canadian cattle, a uniform distribution of scenario probabilities is a conservative (i.e., status quo favoring) prior distribution – one that is biased against taking action. Yet, comparison of the estimated economic repercussions (and, a fortiori, of possible health consequences) from having to test all US Cattle if a new BSE case is found vs. testing only imported Canadian cattle in the US if a BSE case is found and is identified (via tracking information) as of Canadian origin shows that the VOI of tracking information is many times greater than its costs – and that this conclusion is robust to many scientific and market uncertainties, including uncertainties about the correct choice of priors (Cox et al., 2004).

Thus, where a pure precautionary stance might recommend an extreme action now (e.g., to test all cattle immediately), a VOI analysis gives a robust recommendation to collect additional information now (by starting a tracking program for Canadian imports), then act optimally given that information and any future observations (e.g., by banning or testing all Canadian cattle imports only vs. all US cattle in the event of a new confirmed case(s) of BSE. In this case, a precautionary reaction of taking widespread action now (e.g., testing all cattle without necessarily being able to identify their origins) maximizes the probability of heavy economic losses while minimizing ability to identify measures that will effectively protect economic and health goals.

CONCLUSION

Regulators and stakeholders often face decision-making under circumstances about which they are uncertain and in which sciences do not provide sufficient knowledge to permit reliable statistical analysis. Yet, these circumstances often demand early action because the magnitude, severity or irreversibility of potential damage may be too great for an action to be postponed until adequate scientific knowledge becomes available. It follows that societal decision-making requires measures of uncertainty and variability consistent with different levels of information availability. Moreover, some replicable form of cost-benefit balancing (e.g., cost-benefit analysis) should justify the allocation of scarce societal resources.

This paper has addressed the precautionary principle, and some of its variants, by focusing on the legal and scientific basis for representing *risky* outcomes, including the potential for hormetic effects. Probabilistic (Bayesian) reasoning augmented with priors chosen to be biased against the eventually recommended actions (or decision rules) and with sensitivity analyses to establish where robust decision recommendations can be made despite uncertainties (including uncertainty in the priors) provides a potentially useful and practical approach to principled decision-making. This VOI framework acknowledges the contingent nature of precautionary actions and allows for (and exploits) opportunities to modify future decisions in light of new information. Thus, our first conclusion is that the useful aspects of precautionary principles are often subsumed by appropriate VOI analysis, modified to acknowledge uncertainties in probabilities. VOI-based decision analysis may be appropriate to any jurisdiction considering precautionary principles.

We have also determined that the precautionary principle based on causal analyses is consistent with – and requires — enlarging the set of regulatory defaults by including non-linear (e.g., biphasic) dose-response models, rather than limiting that set to linear models. Thus, our second conclusion is that the forms of the precautionary principle we find justifiable, as social calculus, requires increasing the set of regulatory defaults to include non-linear (e.g., biphasic) dose-response models because to exclude them is fundamentally, and paradoxically, underprotective, given the state-of-knowledge and the generalizability of these models. Third, we conclude that quantitative risk analyses are superior to qualitative risk analyses because the latter are inherently insufficient (in terms of error rate coverage) for managing the potential outcomes of actions to be considered under any form of the precautionary principle. We suggest that contingent actions based on the precautionary principle, regardless of its variant, still require justification based on testable hypotheses of causation, peer reviewed evidence, and reliable inference with uncertain probabilities. Removal of the contingency and finalization of the rule, either as a standard or guideline, should follow the traditional procedural and substantive law of the jurisdiction where the rule impacts.

NOTES

1. Gifis, SH, Law Dictionary, 2nd Ed, Barron's Educational Series, Woodbury, NY (1984). As an example, first in time, first in right, is a legal maxim.
2. Heisenberg W, Physics and Philosophy, the revolution of modern science, Harper, NY (1958). A scientific

maxim is Einstein's "God does not play dice," Ibid.

3. Wilsher v. Essex Area Health Authority, 2 WLR 425 [1988], reconfirms the tenet that the burden of proof remains on the plaintiff.
4. Summers v. Tice, 199 P.2d 1 (1948).
5. This "all or nothing" rule originates in Butterfield v. Forrester, 11 East 60 [1809]
6. Leyland Shipping Co. v. Norwich Union Fire Insurance Society [1918] A.C. 350, at 370.
7. In re Polemis and Furness, Withy and Co. [1921] 3 K. B. 560.
8. Haynes v. Harwood [1935] 1 K. B. 146, at 156.
9. Yorkshire Dale Steamship Co. v. Minister of War Transport [1942] A. C. 691.
10. McGhee v. National Coal Board [1972] All ER 1008.
11. (1993) QBD (1993), Current Law 2978, The Guardian, October 15, 1993.
12. Restatement (II) Section 431, comment a.
13. In Re Bendectin Litigation, 857 F2d. 290 (6th Cir. 1988); Thropp v. Bache Halsey Stuart Shields Inc., 650 F.2d. 817 (6th Cir. 1981).
14. Restatement (II) Section, p. 442.
15. 458 F. Supp. 338 (S.D.N.Y. 1978).
16. 458 F.Supp. 338 (S.D.N.Y., 1978). The original Table is Probabilities Associated with Various Standards of Proof Judges in the Eastern District of New York, at 410. In that Table, the percentage sign is included after each numerical value (unless unnecessary); for convenience we added the % sign in the headings, but omitted it from the numerical values in the table.
17. Gastwirth, "Statistical Reasoning in the Legal Setting," Am. Statistician, 46:55, (1992).
18. At 411, citing Wigmore, Evidence, (3rd ed. 1940) § 2497, p. 325.
19. At 411, citing Starkie, Law of Evidence, 9th Am. Ed. by Sharswood (1869) at 753 - 754.
20. At 411, citing Bentham, Rationale of Judicial Evidence, Ch. VI, 71 ff (1827).
21. 15 USC §2601(c); Corrosion Proof Fittings v. US EPA, 947 F.2d 1201 (5th Cir. 1991)
22. Motor Vehicle Manufacturers' Assoc. v. State Farm Mutual Automobile Insurance Co., 463 U.S. 29 (1983).
23. 100 S.Ct. 2844 (1980).
24. 29 CFR 1910.1028, 52 FR 34460, 345676.
25. City of Brookings Municipal Tel. Co. v. FCC, 822 F2d 1153 (D.C.Cir. 1987), in Breyer SG, RB Stewart, CR Sunstein, ML Spitzer, Administrative Law and regulatory Policy: problems, text, and cases, Aspen Law, NY (1999). Clearly, what constitutes a reasonable set of options for one court can be unreasonable for another; nonetheless, some guidance does exist to bound the set by excluding fanciful options.
26. Vermont Yankee Nuclear Power Corp. v. NRDC, 435 U.S. 519 (1977), in which the Supreme Court held that the failure of an agency to include "every alternative … regardless of uncommon or unknown" does not invalidate that agency's rulemaking.
27. Baltimore Gas & Electric Co. v. NRDC, 462 U.S. 976 (1983).
28. Breyer SG, RB Stewart, CR Sunstein, ML Spitzer, Administrative Law and regulatory Policy: problems, text, and cases, Aspen Law, NY (1999).
29. 831 F.2d 1108 (D.C. Cir. 1987)
30. Chevron, Inc., v. NRDC, 467 U.S. 837 (1984).
31. American Lung Assoc. v. Browner, 884 F. Sup. 345 (D. Ariz. 1994).
32. 42 U.S.C. Sect. 7409(a).
33. No. 99-1257, Feb. 27, 2000.
34. FindLaw Const. Law Center (2001).
35. Frye v. U.S., 293 F. 1013 (D.C.Cir. 1923)
36. Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S.579 (1993).
37. General electric Co., et al., v. Robert K. Joiner et Ux., 66 US Law Week 4036 (1997).
38. US v. Abel, 469 U.S. 45 (1984), Beech Aircraft Corp., v. Rainey, 488 U.S. 153 (1988) for two different holdings concerning the abuse of discretion standard.
39. We do not discuss the Federal Rules of Evidence; the cases cited give the relevant information.

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