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Just who is at risk? The ethics of environmental regulation

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Abstract

The willingness to view risk as part of daily life has vanished. A risk-averse mindset among environmental regulators engenders confusion between the ethics of intention and the ethics of consequence, leading to the elevation of the precautionary principle with unintended and often unfortunate outcomes. Environmental risk assessment is conservative, but the actual level of conservatism cannot be determined. High-end exposure assumptions and current toxicity criteria from the USEPA, based on linear extrapolation for carcinogens and default uncertainty factors for systemic toxicants, obscure the degree of conservatism in risk assessments. Ideally, one could choose a percentile of the target population to include within environmental standards, but this choice is complicated by the food, pharmaceutical and advertising industries, whose activities, inadvertent or not, often promote maladaptive and unhealthy lifestyle choices. There has lately been much discussion about background exposures and disease processes and their potential to increase the risk from environmental chemicals. Should these background exposures or disease processes, especially those associated with maladaptive individual choices, be included as part of a regulatory risk evaluation? A significant ethical question is whether environmental regulation should protect those pursuing a self-destructive lifestyle that may add to or synergize with otherwise innocuous environmental exposures. Choosing a target percentile of protection would provide an increased level of transparency and the flexibility to choose a higher or lower percentile if such a choice is warranted. Transparency and flexibility will lead to more responsive environmental regulation that balances protection of public health and the stewardship of societal resources.

Keywords

human toxicology, pollution/environmental toxicology, risk assessment, risk communication, regulatory toxicology

The ethics of environmental regulation

Theories of ethics and society

There are two basic directions in ethics – ethics of the mind that justifies an action by reference to intention and ethics of the consequence that justifies an action by reference to results.[1] These are also known as deontological and teleological ethical theories, respectively.[2,3]

For example, telling the truth is considered by many to be 'the right thing to do' regardless of consequences and is an example of deontological ethics. Kant's categorical imperative represents a moral obligation stemming from the duty to 'do good' and, as such, is also an expression of deontological ethics. Kant noted that people may perform good deeds for bad reasons (e.g., egotism, attaining social prominence, etc.), and, under deontological ethics, the deeds would have no moral worth.[4]

On the other hand, teleological ethics is expressed as utilitarianism that supports material benefit (e.g., money, pleasure, food, survival) as an appropriate end. In *Leviathan*, Thomas Hobbes opines that utilitarianism requires that man accede to a sovereign authority. Individual utilitarianism gives every man or woman the license to possess everything in the world, thus leading to conflict and lives that are 'solitary, poor, nasty, brutish and short.' In Hobbes' view of this social contract, man gives up individual utilitarianism for that of the society.[5]

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In *Two Treatises of Government*, John Locke echoes some of Hobbes' ideas, except that he believes that human nature is based more on reason and tolerance than on selfishness. Every man or woman has a right to defend his life, health, liberty and possessions, but consents in other areas to the will of a sovereign authority. Locke's ideas had a profound influence on the thinking of the founders of the United States, and the democratic society of the United States is a clear example of a civil society ruled by an elected sovereign whose authority depends on the consent of the governed.[6]

While Locke championed the individual, Jean-Jacques Rousseau conceived the idea of a 'general will' in which an individual puts aside his own will or egoism in favor of the collective social interest. In *The Social Contract or Principles of Political Right*, Rousseau developed the idea of the social contract. This idea can be summarized as follows: each of us puts his person and all his power in common under the supreme direction of the general will and in a body we receive each member as an indivisible part of the whole.[7]

The philosophy of utilitarianism is generally credited to Jeremy Bentham, who, in his *Introduction to Principles and Morals of Legislation*, attempted to relate the functioning of government to moral and ethical principles. Bentham wished to create a code of law based on the principle of utilitarianism, the embrace of policies that would produce 'the greatest happiness for the greatest number.'[8]

Utilitarianism and utilitarian ethics are based on the idea that the moral worth of an action is solely related to its contribution to the overall 'good.' It is an obvious application of teleological ethics. Following Bentham, John Stuart Mill furthered the development of utilitarianism, arguing in his short work *Utilitarianism* that cultural, intellectual and spiritual pleasures are of greater value than hedonic or physical pleasures and the sole reason that a member of a civilized society can be brought to compliance against his or her will by the power of the government is to prevent harm to others.[9,10]

While there are strong arguments for teleological ethics, and while utilitarianism forms the basis of modern decision theory and decision analysis, the ultimate expression of utilitarianism is that the moral worth of an action is solely determined by its consequences or, put simply, the end justifies the means. Those with a deontological bent may believe that the position of the end justifying the means is not a moral position because the acts needed to achieve these ends are immoral (e.g., war, torture).

The ethical basis of environmental regulation

In general, utilitarianism or teleological ethics provides the basis of environmental regulation – there is no intrinsic common good in setting an environmental regulation, such as a maximum contaminant level (MCL) in drinking water, at a particular level; instead, the common good arises from the protection inherent in the regulation – the consequent avoidance of human disease and the sustainability of the environment. This position is consistent with the principles of Hobbes, Locke, Rousseau, Bentham and Mills.[5-10] Environmental standards are an expression of the utilitarianism inherent in the social contract – these standards seek to provide protection of public health without undue impact to the economic activities of the regulated community whose products and activities also increase the common good.

However, deontological ethics and teleological ethics have become woven together in a confusing and often inexplicable way to support risk-based environmental regulation. At first glance, risk-based environmental regulation seems to espouse teleological utilitarian ethics in an implicit fashion – often, the goal of this regulation is to seek a democratic balance between competing agendas using risk assessment as one of many sources of decision support information. However, many view the risk assessment process as excessively complex, antagonistic to strong environmental protection and fundamentally paternalistic because of the hidden assumptions that have the effect of disenfranchising stakeholders who lack sufficient expertise. A survey in the 1990s revealed that environmental groups were uniform in their disdain, disbelief and skepticism about the process of risk assessment, and risk assessment came to be seen as fundamentally undemocratic.[11,12]

Lack of expertise is not the only factor that drives the embrace of deontological ethics. Of likely greater influence is the uncertainty associated with risk assessment and the increasing risk aversion in modern society. Much of the conservatism inherent in risk assessment is based on this embrace of deontological ethics expressed by the precautionary principle that some find more appealing than the difficult task of balancing competing agendas in a way that attempts to be fair and democratic.

With regard to the setting of environmental regulations, if a regulatory agency chooses the 95th percentile of risk as the basis of a standard, then this choice implicitly expresses the ethics of consequence – that

5% of the population will experience a predicted risk greater than regulatory levels of concern and that this choice is appropriate. On the other hand, some might argue that the choice of the 95th percentile means that in actuality 100% of the population will be included in the standard because risk assessment is already a highly conservative process, and the choice of a high percentile implicitly expresses the ethics of intention.

The Precautionary Principle

The precautionary principle was first given voice at the Rio Declaration of 1992.

> . . . 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.

At first glance, it would seem that the ethics of the consequence provides the basis of the precautionary principle – 'Better safe than sorry!' However, application of the precautionary principle such as acting before sufficient information is available or failing to consider all available scientific information may be viewed as an expression of deontological ethics. The precautionary principle is often recommended as the basis of regulation without consideration of both potential risks and potential benefits; in some cases, the consequences of this imperative to 'just do something' are worse than the consequences of inaction.

The precautionary principle was given voice to encourage policies that protect human health and the environment in the face of uncertain risks.[13] Many champions of the precautionary principle indicate that the ethics of the consequence are embodied in the application of this principle.[14-19] However, the precautionary principle, as applied, is based on the ethics of intention, and, as will be seen below, the application of this principle fails to meet the goal of true democratic utilitarianism because of unintended consequences.

Applying the precautionary principle leads to unintended consequences

Decision analysis is based on maximization of a utility function relating the choice of various actions to the likely consequences of each action.[20-27] Differing perceptions of the state of knowledge regarding both the risks and benefits of a regulatory action will likely complicate the decision.[28-31]

What is forgotten by the proponents of the precautionary principle is the consequence to society of a 'knee-jerk' response. In today's world, risk managers in many fields suffer from tunnel vision – Wall Street's dependence on complex models and the ensuing financial meltdown of 2007 is ample evidence.

The same tunnel vision is evident in some areas of environmental regulation where the legacy of the twentieth century view of environmental risk is tantamount to an open invitation to act – to 'just do something' – without consideration of consequences and without explicit accounting of risks, costs, benefits and uncertainties. To counter this invitation, Dr John Graham, as head of the Office of Management and Budget, issued *Circular A-4*, which called for demonstrated cost-effectiveness of regulatory decisions, including formal probabilistic analysis for decisions with an impact of more than a billion dollars.[32] This document indicates that discovery of which decision yields the greatest net societal economic benefit provides useful information to decision-makers even when economic efficiency is not the primary public policy objective. The document also recommends that risk-benefit-cost analysis be applied to decisions in many areas. *Circular A-4* was an effort to provide a more reasoned alternative to the precautionary principle.

There may be some appropriate uses of the precautionary principle[2,17,33]; however, in many cases, the lack of understanding of the consequences leads to poor decisions when the decision-makers assume that rightness of intention (deontological ethics) is a sufficient basis and justification for a decision and rely on the precautionary principle to support their choice. As noted, the danger in this reliance is the occurrence of unintended consequences because decision-makers who apply the principle to support an action often and incorrectly believe that their understanding of the consequences is sufficient for the decision.

Nonetheless, there is a continuum of knowledge about the consequences of a decision. If regulators concluded that regulation was unwarranted because the potential negative consequences would not outweigh the benefits, this action would constitute teleological ethics. However, not only the content of the decision support information but also its quality must be considered.

As practiced today, environmental risk assessment is an expression of the ethics of intention – the sum total of the many conservative decisions regarding exposure and toxicity that support a larger regulatory

decision indeed constitute an expression of the deontological ethics embodied in the precautionary principle. The excessive reliance on highly conservative default assumptions regarding both exposure and toxicity is an application of the precautionary principle, and it is frankly dishonest to masquerade this as either utilitarianism or good science.

Example #1 – Corticosteroids and head injury. Although corticosteroids were once used routinely to treat traumatic head injury, ostensibly to reduce intracranial pressure, their use actually increased patient mortality. Physicians used corticosteroids until the 1980s when managed care organizations demanded a review of the practice on the basis of cost. The collective belief of physicians turned out to be wrong; the Corticosteroid Randomisation After Significant Head injury (CRASH) study found a statistically significant increase in deaths among the group treated with corticosteroids.[34,35]

Example #2 – Use of triclosan in personal care products. Triclosan is an anti-bacterial agent found in a plethora of personal care products. As a disinfectant, it has proven useful as an anti-malarial and an oral-hygiene product.[36,37] In neonatal intensive care units, triclosan use has been associated with a significant reduction in methicilin-resistant *Staphylococcus aureus* infections (MRSA) and a diminished need for antibiotics.[38]

However, triclosan has very recently been shown to reduce serum testosterone and thyroid hormones in juvenile male rats.[39] It is noteworthy however that the US population has measurable concentrations of triclosan in urine for all age groups. The highest concentrations occur in those 20−29 years, possibly due to greater use of personal care products.[40]

This emerging picture of triclosan begs the question of how to balance both the increase in dental caries and consequent individual and societal cost, and the likely increase in infant mortality from nosocomial infections and consequent emotional distress of the families with the potential of triclosan to be an endocrine disrupting chemical. It remains to be seen how the risk-benefit analysis and possible future regulation of triclosan proceeds.

Example #3 – Non-steroidal anti-inflammatory drug (NSAID) use and heart attacks. NSAIDs have been used for more than 50 years to control pain in those suffering osteoarthritis or rheumatoid arthritis. NSAIDs such as aspirin or ibuprofen also cause adverse gastrointestinal effects such as ulcers. This concern led to the development of cyclooxygenase 2 (COX-2) inhibitors. However, COX-2 inhibitors significantly increase cardiovascular risk.[41-43] A recent compilation of clinic studies and meta-analyses concluded that current data are insufficient to support the development of evidence-based clinical guidelines.[44] The history of the choice of pain medications for arthritis sufferers and increased heart attack risk provides an example of 'you don't know what you don't know.' The best intentions and the urge to act may lead to catastrophic consequences and demonstrates the danger in espousing the precautionary principle.

Applying utilitarianism and the ethics of consequence to environmental regulation

As discussed, environmental risk assessment, as practiced by regulatory agencies, ostensibly uses the ethics of the consequence as the basis for decisions. There are statutory levels of predicted risk from a defined activity or source that must be met (e.g., a one-in-a-million cancer risk, hazard index less than one). The use of such quantitative risk targets provides the flavor of the ethics of the consequence; however, in practice, the choices of the details of risk assessment become expressions of the precautionary principle and thus, the application of the ethics of intention because of three reasons: (1) the utilitarianism of risk-cost-benefit analysis is not considered by regulatory personnel, (2) excessively conservative default values are used to characterize both exposure and toxicity and (3) many environmental regulatory personnel are highly risk-averse and will explicitly 'err on the side of caution.'

To be clear, it is important to maintain a separation of risk assessment and risk management.[45-47] There is a need for dispassionate interpretation of scientific information for a credible risk analysis. Societal, political or economic considerations have no role in a science-based risk analysis. Consideration or quantification of uncertainty or variability in toxicological and exposure assessment used in environmental risk assessments should be based on best-available science. However, the actual regulatory decision will be based on a mélange of scientific, economic, political and societal factors, and this inevitable balancing of agendas is a necessary and vital part of decision making in a democratic society.

There is another major sticking point with the application of the ethics of the consequence to

environmental regulation. Put simply, should the predictions of risk be equivalent to actual impacts? No regulatory decision-maker would be comfortable with a body count as the basis of a decision, and thus, it is not difficult at all to understand why regulators are risk-averse. Nonetheless, because of pervasive risk-averse attitudes, the ethics of intention become confused with the ethics of consequence. For example, given that the cancer risk of living in the developed world is around one-in-four and the difficulty of attributing cancers to environmental factors, the choice of a one-in-a-million as risk target is unobservable and unrealistic.[48-51]

Conservatism in cancer dose-response assessment. The default assumption for cancer risk assessment is that carcinogens are mutagenic and genotoxic.[52] The use of the linear assumption for low-dose extrapolation is based on the notion that a single molecule of a carcinogen could conceivably be sufficient to produce a mutation that would lead to cancer and that exposure to environmental carcinogens adds to ongoing background exposures and disease processes.[53,54] The presentation of the linearized multistage model was compelling to regulators because the methodology was loosely based on biology and incorporated a 'safety' factor by the use of either the 95% upper confidence limit (UCL) on the slope of the low-dose linear portion of the dose-response curve or the 95% lower confidence limit on the dose associated with a chosen point of departure.[55,56] While highly protective, the use of these statistical confidence limits adds an unknown and unquantifiable degree of conservatism to cancer risk assessment. Too often, cancer risk estimates are driven by deficiencies in the design of animal bioassays selected rather than any underlying biology.

A larger issue is the assumption of linearity for low-dose extrapolation. In 2008, the National Research Council (NRC) released a report titled *Science and Decisions: Advancing Risk Assessment*.[57] Regarding the dose-response assessment, the NRC report recommended that the approach to risk assessment for both cancer and non-cancer endpoints be unified. In this context, the reference-dose concept based on a threshold would be abandoned in favor of the risk-specific dose (RSD) and linear extrapolation would be used for both cancer and non-cancer effects.

The writers of the NRC report had a blind spot when it came to the existence of biological thresholds.[57] Thresholds are inherent in the response of all biological systems to stressors due to the physiological mechanisms that maintain homeostasis within a narrow range. The assumption of low-dose linearity for all chemicals and all effects depends on assumptions about mode of action that are not supported by biology.[58-61] Organisms often have highly redundant systems that provide an ample buffer for maintaining homeostasis. However, when one or more of an organism's capacities are exceeded, a departure from homeostasis, usually in the form of disease or death, occurs. The idea of thresholds is implicit in Paracelsus' dictum that the dose makes the poison.[62] The lack of consistency between the linear assumption and accumulated knowledge of biology is discussed further below.

While economists can determine the societal and individual cost of cancer and can determine the societal cost of hazardous waste regulation,[63] the cancer slope factor implemented using low dose linear extrapolation and statistical confidence limits is not an appropriate tool to implement an approach based on true utilitarianism and teleological ethics.

Conservatism in non-cancer dose-response assessment. Non-cancer toxicity criteria are generally based on some measure of a no-effect or lowest effect level in animals and extrapolated to humans using uncertainty or safety factors.[64-68] Hence, these toxicity criteria are non-linear and based on the fact that thresholds apparent in animal bioassays also occur in humans.

The definition of uncertainty factors (UFs) has been extended from single value point estimates to policy-based probability distributions.[69-71] More recently, analyses of human variability based on observed effect levels of therapeutic drugs has improved the understanding of the distributions used to model UFs.[72-75] Some have suggested a more flexible framework to replace default values for UFs with values related to specific metabolic pathways.[76] These could be used when detailed chemical-specific toxicokinetic or toxicodynamic data are not available. The International Programme on Chemical Safety (IPCS) provides guidelines for the use of chemical-specific adjustment factors.[77] Unfortunately, the work of some of the leaders in this area indicates that the use of the default UF value of 10 will be continued into the foreseeable future.[78]

The clear advantage to regulators for the use of default UFs in combination with one another is the high confidence that risk will be overestimated and

that no actual impacts will occur. However, the use of multiple default UFs is an expression of the precautionary principle and, as such, is inconsistent with utilitarianism and teleological ethics.

In the United States, the Agency for Toxic Substances and Disease Registry (ATSDR) is part of the Centers for Disease Control and develops health assessments to determine whether individuals living or working near hazardous waste sites will experience health effects. Minimum risk levels (MRLs) are non-cancer toxicity criteria developed by ATSDR. The process for developing MRLs depends on application of UFs and is identical to US Environmental Protection Agency's (USEPA) process for developing reference doses (RfDs) protective of non-cancer effects in humans.

The RfD concept, while appropriate for the development of protective estimates of the human dose threshold for the purpose of setting environmental media standards, is an inappropriate methodology for assessing actual public health impacts, as practiced by ATSDR. In this regard, both USEPA and ATSDR are applying deontological ethics masked as utilitarianism. The MRLs, toxicity criteria used by ATSDR, are likely orders of magnitude lower than actual human thresholds. RfDs, used by USEPA, are also inconsistent with teleological ethics because their use precludes consideration of both risks and benefits in decision-making.

Reconciling biology with linear dose response. The NRC 2008 report, *Science and Decisions: Advancing Risk Assessment*, seems at first glance to be an expression of utilitarian ethics because it acknowledges that current risk assessment methods are inadequate for risk-benefit-cost analysis.[57,79] The report advocates the use of linear extrapolation for developing toxicity criteria for both cancer and non-cancer endpoints, and suggests that linear extrapolation will be used for the majority of chemicals. The history of the adoption of the linear approach for cancer risk assessment is a cautionary tale about the rise and fall of scientific theories coinciding (or not) with the need to make regulatory decisions.[80]

The choice of linear extrapolation for all chemicals is based on the assumption that because of background exposures or ongoing disease processes and inter-individual variation in the threshold for a given adverse effect, the response of humans to chemical exposures will likely be represented most faithfully by linear low-dose extrapolation. Based on three decades' experience with linear extrapolation for the cancer endpoint, the linear approach almost always produces more restrictive/conservative toxicity criteria than the nonlinear approach.[80] Therefore, the approach to low-dose extrapolation presented in the NRC report will have profound effects upon risk management decisions. As yet, a full discussion of the biological basis for low-dose adjustment, and potential outcomes of adopting the general use of this methodology have not yet occurred.[79,81,82]

The use of linear low-dose extrapolation for all chemicals is inconsistent with the body of biological knowledge about the maintenance of homeostasis, the principles of physical chemistry of reactions of xenobiotics with biological molecules and the growing body of dose-response data using newer high-throughput data and a systems biology conceptual approach. Indeed, the majority of biological data on dose-response suggests that most chemicals, including genotoxic carcinogens such as diethylnitrosamine, exhibit a dose threshold.[83-90]

Continued existence for any organism is a matter of maintaining homeostasis in the face of an unremitting array of a variety of stressors. Organisms have the capacities to deal with many different stressors, but these capacities are finite and their exceedance results in a catastrophic departure from homeostasis, usually in the form of disease or death. Specific aspects of an organism's biology determine these capacities and the associated thresholds.[91]

Chapter 5 of the NRC report about dose response appears in conflict with Chapter 8 about improving the utility of risk assessment.[57] Chapter 8 specifically recommends 'expanding the lens' of risk management from single issue incremental risk focus to a more global perspective of considering risk-risk tradeoffs, public values and risk-benefit analysis. This recommendation is consistent with utilitarian ethics described here. However, the use of linear extrapolation in cancer dose response and, as proposed in Chapter 5, for both cancer and non-cancer dose response is tantamount to a 'thumb on the scale' for risk-risk comparisons or risk-benefit analyses. Risk estimates developed using linear low-dose extrapolation cannot be reconciled with the growing knowledge of the biology of cancer. Hence, these estimates lack scientific integrity and cannot be considered consistent with the teleological ethics espoused in Chapter 8 of the NRC report.

A valid risk-cost-benefit analysis cannot currently be performed using the RfD or the cancer slope factor

and neither type of toxicity criterion is an appropriate tool to implement an approach based on true utilitarianism and teleological ethics.[92]

Regulating risks versus regulating impacts

Risk assessment utilizes scientific information, but it is not science. The struggle for honest regulators is knowing how well the predictions of a risk assessment, with all their inherent uncertainty, can serve as an appropriate basis for the setting of environmental standards. Are these risk predictions sufficiently informed and sufficiently fair to all stakeholders to view them as an application of utilitarianism?

A major difficulty with applying utilitarianism and the ethics of the consequence to environmental regulation is whether the predicted or the actual consequence should be the ethical determinant. The predictions involved here constitute the discipline of risk assessment, a discipline that has arisen because of the societal consensus that unregulated exposure to environmental chemicals in food, drugs or environmental media constitutes a potentially unacceptable harm. Risk and harm are not the same but have become confused in the minds of some regulators and the minds of some within the general public.

The results of any predictive activity, including risk assessment, will always depart from the actual consequences. Environmental regulators serve two masters; they must provide an appropriate level of protection for the general public and they must also serve as stewards for societal resources. The balance to be achieved by environmental regulation is that between the cost of harm from existing contamination versus the cost of cleanup to a protective environmental standard. From the standpoint of all the governed society, the best decision (that with the greatest utility) results when a balance is achieved between the cost of cleanup and the cost of actual harm. Implicit in environmental regulation is the view that the predicted consequence (i.e. the risk) and not the actual impact constitutes the ethical consequence and thus serves as the determinant or goal in the application of teleological ethics.

Given the lack of uniformity in the risk assessment process and resulting wide variation between the predicted consequences and the actual impacts, one can easily understand why members of the regulated community or taxpayers who bear the cost of cleanup are highly skeptical of the many conservative assumptions in risk assessment. Without a clear conceptual path from predicted risk to actual impacts and a clear statement that predicted risk is the most appropriate regulatory tool, the regulated community tends to perceive risk assessment as tool for more unnecessary regulation rather than an action based on teleological ethics and true utilitarianism.

Compounding conservatism

Uncertainty and conservatism in exposure

USEPA's Superfund program uses the concept of reasonable maximum exposure (RME) in choosing estimated risk levels upon which to base cleanup decisions and as a basis for the calculation of environmental media standards. *RAGS Part A Volume I* from USEPA introduced the RME concept.[93]

As part of the definition of RME, a number of exposure factors were chosen as upper percentile values whereas body weight was chosen as a central value. The RME is a clear example of compounding conservatism in exposure.

The RME concept was also presented in the 1992 *Final Guidelines for Exposure Assessment* by the Risk Assessment Forum.[94] The Guidelines state that the upper end of the distribution of risk should be characterized and high-end estimates of individual risk, such as the hypothetical RME individual, should fall at the 90th percentile or above. Additionally, the Guidelines provide a detailed and cogent discussion of uncertainty assessment that concludes:

> *It is fundamental to exposure assessment that assessors have a clear distinction between the variability of exposures received by individuals in a population, and the uncertainty of the data and physical parameters used in calculating exposure.*

The discussion of compounding conservatism was prominent in the scientific literature during the 1990s. David Burmaster of Alceon in Cambridge, MA, USA, was one of the most vocal critics of USEPA's risk assessment policies at that time. Burmaster was a man ahead of his time and suffered a great deal of frustration when USEPA risk assessors turned a deaf ear to his requests that they consider probabilistic risk assessment as an antidote to compounding conservatism.[95-100]

RME: is it reasonable?. In 1992, the use of a single-point estimate of risk and associated lack of transparency in risk-based decision-making led to the issuance of a memorandum from F. Henry Habicht,

then deputy administrator of USEPA. This memo was the first official statement from USEPA that the 'standard operating procedure' for risk assessment failed to convey the full picture of risks, especially when the results of a complex and time-consuming assessment were transmitted to decision makers and the public as a single number.[101] This point was made quite eloquently as follows:

> Specifically, although a great deal of careful analysis and scientific judgment goes into the development of EPA risk assessments, significant information is often omitted as the results of the assessment are passed along in the decision-making process. Often, when risk information is presented to the ultimate decision-maker and to the public, the results have been boiled down to a point estimate of risk. Such 'short hand' approaches to risk assessment do not fully convey the range of information considered and used in developing the assessment. In short, informative risk characterization clarifies the scientific basis for EPA decisions, while numbers alone do not give a true picture of the assessment.

This quote from the 'Habicht memo' conveys exactly the difficulty with the use of point estimate numerical standards. While such standards provide great convenience, they are often used in an indiscriminate fashion and are not fully transparent.

Estimates of the degree of conservatism related to exposure suggest that with three or more exposure factors that appear roughly lognormal in their distributions and set at their respective 95th percentiles, the resulting percentile of their product is greater than the 99.9th percentile.[97,100,102]

In spite of the inherent conservatism noted above, the concept of 'Reasonable Maximum Exposure' has served the field of risk assessment very well over time.[93,94] Although, in many cases, the application of the RME concept is flawed and will require additional thought to consider biomonitoring and biomarker data, the concept itself remains a valid one.[103] The reason for the long success of the RME concept is that it can be applied to all risk assessment methodologies.

Uncertainty and conservatism in toxicity

It is clear that the use of UFs in the derivation of the RfD adds an unknown degree of conservatism. Similarly, the use of the 95% UCL on the slope of the dose-response curve used as a cancer potency factor is also conservative at an unknown level. As noted earlier, the conservatism associated with the UCL estimate of the slope may depend heavily on the study design and other factors rather than the toxicology or biology of the particular substance.

This inability to quantify the uncertainty associated with toxicity criteria is one of the factors that led the National Research Council to produce *Science and Decisions: Advancing Risk Assessment* in late 2008.[57] One of the goals of this report is to address this issue of the unknown degree of uncertainty (and thus an unknown degree of conservatism) in the toxicity assessment. As discussed, this report suggests that linear extrapolation should be used for both cancer and non-cancer endpoints to be able to estimate RSDs for a given level of effect within a hypothetical population. The stated goal of this change is to better inform decision makers.[57]

Dose-response assessment and the 'RMS' concept. It is unfortunate that there have been no considerations similar to the RME concept to identify the individual representing 'reasonable maximum susceptibility' (RMS). Presently, there is a unique opportunity for some regulatory body to create the concept of RMS for the dose-response side of risk assessment. The RMS concept would likely have the staying power and regulatory 'clout' as the RME concept.

There is growing recognition among regulators of the need to incorporate consideration of human variability and uncertainty about our knowledge into both the exposure assessment and dose-response assessment.[104] Recently, distributions of UFs have been used to estimate probabilistic RfDs.[69,70,105] However, at this point in time, there is no consistent methodology for the application of probabilistic methods to the dose-response assessment, and the regulatory implications of these efforts remain unclear.

Variation in human susceptibility. One of the thorniest problems in risk assessment is the understanding of the variation in human susceptibility to cancer and environmental carcinogens. This variation may depend on genetic factors, biological differences based on age or other non-heritable factors, lifestyle choices, diet and other factors.

A number of genetic factors influence the variation in susceptibility; these include genes associated with P450 enzymes, glutathione transferases, the p53 cell cycle regulatory protein and others.[106-108] For some time, it has been known that genetic polymorphisms played a role in alcohol metabolism.[109] Only recently has the role of genetic factors in the variation of human susceptibility to cancer come to be

appreciated.[110-125] Dietary preferences have been shown to affect susceptibility to colo-rectal cancer and susceptibility to arsenic-induced cancers.[126-128]

It is important to note that genetic variations in susceptibility are not the same as the distinction between genotoxic and epigenetic modes of action of carcinogens.[52,129,130] USEPA recommends, appropriately, the use a non-linear or threshold approach for chemicals for which the knowledge of the mode of action clearly suggests that such an approach is warranted.[52,131-135]

Incorporation of human variation into risk assessment is an enormously difficult task and has a number of possible societal consequences. Variation in cancer risk for humans was introduced to the field of risk assessment as individual time-to-tumor.[136] These ideas led to the recognition that environmental standards would likely leave some proportion, albeit small, of the target population unprotected.[137] Variations in DNA repair capacity and cell-cycle control may affect both the shape of the dose-response curve for DNA reactive carcinogens and, consequently, the individual threshold for a given carcinogen.[138,139] Even if a chemical has a known non-genotoxic mechanism, individual variation may tend to linearize the population dose-response curve.[140] In such a case, it may prove difficult to define a level of protection as a given percentile or proportion of the target population.[140-144]

One hears the term 'sensitive subpopulation' used uncritically among risk practitioners. For many, this term has come to mean either children or the elderly, but it is not correct to use the term so uncritically. For example, very young children have not developed the metabolic capacity of the mixed function oxidases in the liver as have adults. Thus, children have different pharmacokinetics than adults, and, for this reason, children could actually be less sensitive to some xenobiotic chemicals.[145]

An example of a true sensitive subpopulation would be individuals with deficiencies in glucuronidation such as Crigler-Najjar syndrome or Gilbert's syndrome.[146] These are related to genetic variability of uridine 5′-diphospho-glucuronosyltransferases (UDPGT). Individuals with Gilbert's syndrome have mild, chronic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis that manifests most often as neonatal jaundice.[147-150] Individuals with Gilbert's syndrome may be more sensitive to some xenobiotics that are excreted via glucuronidation. Crigler-Najjar syndrome is more serious and can produce kernicterus that is either fatal or leads to neurological impairment

Were perfect knowledge of the variation in individual susceptibility available, then the regulation of environmental risk would be possible. Almost all governmental environmental regulatory agencies use the default low-dose linear assumption in the calculation of numerical cancer potency factors. On one hand, the assumption of linearity can be considered as teleological ethics because scientific information (i.e., dose-response data) is used to obtain a protective human risk estimate. On the other hand, the application of the low-dose linear assumption to all chemicals can also be considered deontological ethics because it will almost always result in a risk assessment with a high but unknown degree of conservatism. More importantly, low-dose linearity is an expression of the precautionary principle and is inconsistent with the accumulated knowledge of biology.

This reflex to protect against cancer is hardly surprising. Fear of cancer has become ingrained in western society.[151] This fear is reflected in the adoption of the Delaney Clause by the US Congress in 1958 that concludes that no food additive that has been shown to induce cancer in man or experimental animals can be considered safe.[62] This fear is also demonstrated by the ire of Congressman Andy McGuire who represented New Jersey's 7th district from 1975 to 1981 upon learning that nitrosamines were present in pesticide samples that USEPA had failed to withdraw from the marketplace.[152]

Lifestyle, freedom of choice and regulation. Factors based on lifestyle choices can predispose certain individuals to cancer.[153,154] How can a regulatory agency reconcile the freedom of choice in western societies, including the freedoms to use tobacco products, to drink unhealthy amounts of alcohol, to eat an unhealthy diet, to eschew physical exercise or to text while driving an automobile, with the need for regulatory protection? Is it fair to use society's resources to reduce cancer risk from environmental chemicals in a three-pack a day smoker who will likely contract cancer anyway? Is it fair that government regulators attempt to regulate and possibly reduce cancer risks from environmental exposures when the same sovereign governments treat much higher cancer risk estimates due to workplace exposures as acceptable?

Some of us may be unlucky to have inherited genetic factors that predispose us to disease – there

are those in the population who, through no fault of their own, are more susceptible to the effects of chemicals in the environment. For these unlucky few, development of a standard that protects less than 100% of the population is democratic tyranny – the foisting of the wishes of the majority upon the unlucky minority, who happen to possess greater genetic susceptibility.

Make no mistake – attaining environmental standards has a cost. If a regulated entity must comply with an overly restrictive standard, then the societal benefits ensuing from that entity will be reduced. A regulatory agency may take a precautionary approach (deontological ethics) and as a result, develop standards that have a high confidence level of being protective of the entire target population. This approach will not be welcomed by the regulated community because this community sees their resources being wasted in the attempt to lower non-existent risks because of the conservatism in risk assessment or to control uncontrollable risks in those whose maladaptive lifestyle choices predispose them to adverse outcomes.

The difficulty in reconciling freedom of choice with regulation has been recently highlighted by the controversy engendered by the 2008−2009 report of the President's Cancer Panel, released in May of 2010. The report suggested that the prevailing regulatory approach to environmental chemicals and cancer was reactionary rather than precautionary. The report also stated that the 'true burden of environmentally induced cancer has been grossly underestimated.'[155] The report was immediately criticized by Dr Michael J. Thun, vice president, emeritus of Epidemiology and Surveillance Research of the American Cancer Society. Dr Thun stated that the report was unbalanced in its perspective for dismissing prevention efforts aimed at known causes of cancer such as tobacco, obesity, alcohol, infections, hormones and sunlight. Dr Thun also stated that the report did not represent the scientific consensus on environmentally induced cancer.[156]

Dr Thun is correct − in terms of bang for the buck, health risks in the US population might be reduced to a much greater extent by targeting resources towards smoking cessation and promotion of healthy lifestyles than toward regulation of environmental chemicals. Given the content of the President's Cancer Panel report, concerns expressed by the US government about the rising cost of health care amount to nothing more than talk.

Because of the inherent conservatism of current risk assessment practices, the regulated community likely bears an excessive burden resulting from both regulation based on phantom risks and inclusion within the protection of an environmental standard those whose maladaptive behavior puts them at greater risk. At the 2010 meeting of the Society of Toxicology, some USEPA staffers used the term 'obesogen,' presumably meaning a chemical that causes people to get fat. How much of a societal burden is the need to target resources toward health care for the treatment of lifestyle diseases? Apparently, both the President's Cancer Panel and USEPA would absolve people of the responsibility of these maladaptive lifestyle choices by placing the responsibility for lifestyle-related diseases on environmental chemicals. Today's teenagers put it most aptly – 'That's so not fair!'

Does everyone want protection?

It is no secret that lifestyle choices predispose one to disease. The epidemic of obesity, metabolic syndrome and type 2 diabetes suggests that a western diet high in animal fats is not healthy. T. Colin Campbell, a Virginia Tech professor, was invited to participate in a very large epidemiological study by the Chinese government in the 1980s during the initial phase of Chinese urbanization. Known as the China Study and dubbed by the New York Times as the 'Grand Prix of Epidemiology,' this study demonstrated more than 8000 statistically significant associations between various dietary factors and disease.[157]

Competing agendas – environmental regulation, medicine, the food industry and the pharmaceutical industry. The health care industry has been among the slowest to admit the relationship between lifestyle and disease. For example, the prestigious *Journal of the American Medical Association* (*JAMA*) used to carry ads for tobacco products. Indeed, there are documented financial ties between the tobacco industry and the pharmaceutical industry.[158] The food industry maintains many lobbying groups whose function is to increase the profits for the industries they represent, regardless of the relationship of these foods to disease. The medical establishment is complicit by omission – a recent issue of *JAMA* devoted solely to medical education (v. 296, 6 September, 2006) did not contain a single article on the role of nutrition in health and disease. In fact, Campbell and Campbell

(2006) make a compelling argument about western diet and lifestyle as a possible cause for the increased rate of breast cancer in western societies when compared with that in China.[157] Their theory is that the higher rates of breast cancer in the West result from about 7 additional years of estrogen exposure in western women because of the lower age of menarche and higher age of menopause, both possibly due to higher consumption of animal fat and the use of female hormones in the production of beef cattle.[159-161]

Birth control pills and post-menopausal estrogen replacement therapy also increase the risk of breast cancer. This is not a story that the pharmaceutical industry or the food industry want to hear; perhaps conspiracy is too strong a word, but the efforts of these industries to increase profits along with government imprimatur of shoddy science and misleading information, such as the President's Cancer Panel report, have the effect of enabling maladaptive and unhealthy behavior and have significantly complicated the understanding of the relationship of disease to environmental factors.

Environmental regulation and lifestyle choices – a cautionary tale from the American South. An example of the complex relationship between exposure to environmental chemicals, lifestyle choices, competing and often hidden agendas, and the role of environmental regulation recently occurred in Anniston, Alabama. In 2003, the famed attorney Johnny Cochran reached a multimillion dollar settlement between Monsanto, Solutia, Pharmacia and the residents of Anniston, Alabama.[162] The attorneys in the case shared $120 million for their work and the plantiffs received on average about $7000 apiece. The plaintiffs were angry over the amount, which they considered paltry.[163]

The outcome of this lawsuit seemed to set an agenda for ATSDR. The mission of ATSDR, as an agency of the US Department of Health and Human Services, is to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related to toxic substances. ATSDR is directed by congressional mandate to assess the effect on public health of hazardous substances in the environment.

Although ATSDR is not a regulatory agency, the findings of their health assessments may influence regulatory actions by USEPA. How would ATSDR reconcile a finding that health effects would be unlikely for the citizens of Anniston with the outcome of the lawsuit? Apparently, ATSDR felt the need to 'just do something' for the citizens of Anniston.

In May of 2008, a group of epidemiologists working with the Anniston community and funded by ATSDR presented preliminary findings at a workshop sponsored by the National Institute of Environmental Health Science. The overarching research question posed by the ATSDR-funded epidemiologists was whether an association existed between exposure to polychlorinated biphenyls (PCBs) and the occurrence of type 2 diabetes.[164,165] It is noteworthy that to date this work has never been published in a peer-reviewed journal – likely because the work is not of sufficient quality to get through peer review. One of the epidemiologists recently chose to discuss the findings with a reporter from the Anniston Star newspaper.[166] Also, recently, the lead epidemiologist on the project, indicated in a public forum that at least one journal had rejected the work.[167]

One especially disingenuous paper presented at the PCB workshop examined the association between self-reported PCB exposure and self-reported health effects.[168] There was no attempt to relate the self-reported exposure to other more objective measures of exposure, such as soil concentration in an individual's yard or consumption of wild fish and game. The self-reporting of health effects may have been distorted by recent PCB litigation in Anniston and, as with exposure, there was no attempt to relate the self-reported health effects to those associated with PCBs or to sort out confounders such as extent of an individual's involvement with the litigation.

The lack of any reported health effects from PCBs in the Anniston study is interesting in light of peer-reviewed work that found no convincing evidence of any human health effects from PCBs.[169]

The scientific basis for this work in Anniston is the hypothesis relating exposure to dioxin or dioxin-like PCBs to the occurrence of type 2 diabetes. This hypothesis has emerged over the last several years. Because PCBs accumulate in adipose tissue in humans, the hypothesis is that the presence of these chemicals may change the chemical signal, composed of cytokines and adipokines, produced by adipose tissue, and this change is associated with type 2 diabetes.[170,171] Type 2 diabetes is also strongly associated with low birth weight.[172] Low birth weight is associated with maternal smoking.[173] It should be noted that a number of studies attempt to associate human PCB body burden with type 2 diabetes, but

these also fail to consider the individual's birth weight or the maternal lifestyle choices.[174-176]

The scientific basis for ATSDR's work in Anniston was questionable because no attempt was made to sort out the confounders related to type 2 diabetes. The agency did not seem interested in arriving at scientifically supportable conclusions from their work in Anniston. ATSDR hid their true intentions behind a façade of deontological ethics – protecting the citizens of Anniston. Whether this stance was disingenuous or a reflection of the true beliefs of the ATSDR scientists involved will never be known.

It cannot be emphasized too strongly that there are no policy fixes in environmental regulation that can make up for a regulatory agency's intent to apply the precautionary principle and to be perceived as 'just doing something.' As has been already noted, the act of 'just doing something' is very often harmful and almost always without a basis in science.

Compounding conservatism, competing agendas and the impossibility of the choice of a percentile to protect

A Canadian Advisory Committee on Population Health identified determinants of health including age, gender, income, social environment, education, literacy, physical environment, personal health practices, biology and genetics.[177] To this list, one could add the possibility of personal gain through litigation, the desire for profit in the pharmaceutical and medical industries and no doubt, other determinants that have not been considered here. These forces all contribute to frank disease or disease perception. Therefore, a key question for environmental regulators is whether to account for determinants of health unrelated to environmental contamination. One could also ask whether the choice of a level of conservatism should be made as part of a larger integrated effort to prioritize and allocate resources to address the constellation of determinants of health.

When Thomas Hobbes wrote that the role of the sovereign was to save mankind from living lives that were 'solitary, poor, nasty, brutish and short,' most people in Europe at that time struggled to get a sufficient amount to eat, tobacco was unknown and few lived past forty. Cancer and most other modern diseases are multifactorial – environmental factors are one of many contributors to disease. The purpose of environmental regulation is not to save individuals in the target population from their lifestyle choices, risky behavior or poor decisions but from the adverse effects of environmental pollutants; however, in the case of multifactorial diseases, it is impossible to know the extent of the contribution of environmental determinants of health versus those related to lifestyle and other factors, thus complicating immensely environmental regulatory decisions.

The choice of a level of conservatism

Just who is at risk? The ethics of variability and uncertainty

Scientists in the 21st century stand at the threshold of a new understanding of biology – systems biology integrates genomics, proteonomics, metabolomics, transcriptomics and computational methods in an attempt to reach a new understanding applicable to toxicology, risk assessment, medicine and other human endeavors.[178] In fact, USEPA has issued a draft policy on the use of genomic data in risk assessment.[179] There are major differences in human behavior and susceptibility that contribute to an individual's risk. While these factors are recognized, their consideration in environmental risk assessment and their effect on regulatory decisions risk remains unknown.

Risk estimates from USEPA are based on RME and highly conservative toxicity criteria and thus represent the risk to a single hypothetical individual who receives very high exposure and is also highly susceptible to the toxic effects of chemicals.

For the overwhelming majority of chemicals and situations, obtaining accurate predictions of actuarial risk is impossible because of the high level of conservatism in the environmental risk assessment process. From the regulatory perspective, basing environmental regulatory actions on actuarial risk, i.e. disease incidence, is not an appropriate regulatory position whereas adopting a conservative approach in the face of uncertainty is indeed appropriate. The advantage of this high but unknown level of conservatism is the certainty that cleanup levels based on these risk estimates will be protective. However, many in the regulated community see the explosion of biological knowledge being leveraged by the pharmaceutical industry to create new drugs and are rightly dismayed about the gap in the state of the science used to inform drug development and that used to support environmental regulation.

Is it possible to select a percentile or proportion of the population to protect?

If a regulatory agency chooses to develop an environmental standard based on the 95th percentile of risk, one can argue that this choice represents an expression of teleological ethics based on consequences of the choice; these estimates are predicted risks occurring in a hypothetical population, not actual risks incurred by the citizenry. The fact that 5% of this hypothetical population will experience the consequence of a predicted risk greater than regulatory levels of concern represents an appropriate policy choice.

On the other hand, one can argue that the choice of a high-end percentile such as the 95th in an already highly uncertain and conservative process represents an expression of deontological ethics based on intent; the actual level of protection will likely be greater than the 95th percentile and could be at the 99.999th percentile. In terms of deontological ethics, the fact that only a vanishingly tiny fraction of the citizenry would experience a risk greater than regulatory levels of concern is a valid attempt to 'do the right thing' and, as such, may also represent an appropriate policy choice.

Percentile choices by regulatory agencies

US Environmental Protection Agency. The *National Oil and Hazardous Substance Pollution Contingency Plan* (National Contingency Plan or NCP; 40 CFR 300) is the regulation under which the Superfund program operates. The preamble to the NCP indicates that a major objective of the risk assessment is 'to target chemical concentrations associated with levels of risk that will be adequately protective of human health for a particular site.'[180] Because of the high degree of variability in both exposure and susceptibility, it is likely that some small percentile of the target population will remain unprotected even at a risk-based media standard. However, the NCP was silent regarding an acceptable proportion of the target population to protect.

USEPA's *Risk Assessment Guidance for Superfund (RAGS) Part A* indicates that RME estimate for each exposure pathway includes many conservative and upper-bound parameter values and assumptions but, like the NCP, fails to suggest an acceptable percentile to protect.[93]

The 1992 USEPA *Final Guidelines on Exposure Assessment* indicate that a high-end exposure estimate is a plausible estimate of the individual exposure for those persons at the upper end of an exposure distribution. The intent of this designation is to convey an estimate of exposures in the upper range of the distribution but to avoid estimates that are beyond the true distribution. In a footnote, the Guidelines suggest that the high-end exposure estimate should occur between the 90th and 98th percentile.[94]

The Guidelines also address the question of variation in susceptibility and indicates that variability will have been considered as part of the derivation of the dose-response relationship.

RAGS Vol. 3, Guidance on Performing Probabilistic Risk Assessment identifies a percentile range of 90−99.9 that corresponds with RME but cautions against using percentiles higher than the 99th.[181] The reason for this caution is that the extreme percentiles ('tails') of the input distributions are the most uncertain portion of these distributions. This uncertainty in the tails of the input distributions leads in turn to greater uncertainty in the tails of the risk distribution. The magnitude of this uncertainty increases rapidly at the very high percentiles and risk estimates at the extreme tails, such as the 99.9th percentile, may be neither accurate nor plausible.

The Food Quality Protection Act of USEPA's Office of Pesticide Programs implemented *HED SOP 97.2 Interim Guidance for Conducting Aggregate Exposure and Risk Assessments (11/26/97)*.[182] This document supported the use of the 99.9th percentile of exposure for an assessment endpoint for the combined pathways of drinking water, food and residential exposure pathways. In March of 1998, the Scientific Advisory Panel (SAP) for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) reviewed this interim policy and recommended that specific subpopulations be modeled separately. This separation would inform the selection of a lower, less statistically tenuous percentile in calculating a threshold of concern.[183] In the 2001 update to *General Principles for Performing Aggregate Exposure and Risk Assessments*, the policy was changed and a specific percentile was not recommended.[184] Instead, the General Principles documents indicated that the choice of a percentile was a risk management task.

Health Canada. Health Canada's Draft Guidance on site-specific human health risk assessment provides a discussion of what various percentiles of variability in risk might represent for decision-making, but the document stops short of identifying a specific percentile as the basis for risk-based decisions.[185]

REACH. REACH stands for the Registration, Evaluation, Authorisation and Restriction of Chemical substances under regulation EC 1907/2006 of the European Parliament. In general, REACH refrains from the choice of a specific percentile. In the *Technical Notes for Guidance on Human Exposure to Biocidal Products*,[186] the statement is made as follows:

> The correct selection and use of exposure percentiles in a risk assessment is essential in order to avoid excessive conservatism whilst also providing reassurance that highly exposed workers are incorporated into the assessment. As uncertainty increases with small datasets, it is generally the case that a higher percentile such as 90th, 95th or maximum exposure value will be used in place of a more moderate one such as a 75th percentile. Alternatively, a confidence interval may be calculated for a percentile to indicate the level of precision in the value and this supplementary information considered when making the assessment.

The *Technical Guidance Document on Risk Assessment of the European Union* waffles even more in the choice of a percentile. Several core principles are advanced and are summarized as follows:

- Exposure scenarios that are representative of the exposure of a particular (sub)population should, where possible, be described using both reasonable worst case and typical exposures;
- The reasonable worst-case prediction should also consider upper estimates of the extreme use and reasonably foreseeable other uses;
- Exposure as a result of accidents or from abuse shall not be addressed; and,
- Risk reduction/control measures that are already in place should be taken into account.

The attitude of flexibility in the REACH documents represents a very different regulatory viewpoint than that adopted by USEPA.

Science and decisions: advancing risk assessment (NRC, 2008). This draft report was immediately controversial upon its publication. As noted, the report claims that threshold-based toxicity criteria are inadequate for benefit-cost analyses because these nonlinear criteria do not provide the basis for quantifying the magnitude of harm at various exposure levels. The report also indicated that the statistical upper bound on the slope observed in an animal bioassay fails to address human variation. The report goes on to indicate that background exposures and disease processes in the human population, and specifically, in the citizenry being protected, need to be considered in a risk assessment. The report specifically mentions smoking, alcohol consumption and obesity as potential factors that increase human vulnerability to toxicants.

Unfortunately, including these lifestyle choices as factors to be considered in a risk assessment makes all members of the citizenry responsible for the maladaptive choices of some of the members. This position is patently unfair.

In contrast to the NRC report, New York Governor David Patterson's proposed tax on non-diet sodas represents one way in which to make those making such maladaptive choices to pay for the consequences. Also, in March of 2009, the federal cigarette tax was raised from $0.39 to $1.01 per pack. However, it was not made clear that the revenues from this proposed taxes would go towards health care for those who consumed non-diet sodas or for smokers.

Science and Decisions: Advancing Risk Assessment suggests that society at large should bear the consequences of an individual's poor lifestyle decisions. This sentiment is echoed by the report of the President's Cancer Panel that claims that the burden of environmentally induced cancer is underestimated. By absolving the citizenry of the responsibility for the consequences of their decisions, both reports are fundamentally undemocratic.

A voice of reason in government today is that of former University of Chicago law professor, Cass Sunstein, currently the Administrator of the White House Office of Information and Regulatory Affairs (OIRA). Sunstein wrote in his 2005 book, *Laws of Fear: Beyond the Precautionary Principle*,[187] that democratic governments respect liberty and choice but still need to listen to what the people have to say. 'Democratic governments care about facts as well as fears' and need to ensure that 'laws and policies and regulations reduce, and not replicate, these errors to which fearful people are prone.'

It is the obligation of a democratic government to provide valid information to citizens and regulators so that informed choices can be made. Such valid information was not provided in either *Science and Decisions: Advancing Risk Assessment* or the report of the President's Cancer Panel. In sum, the citizenry of a democracy should be free to make maladaptive lifestyle choices – but the consequences of those choices should be theirs alone to bear.

Providing transparency

While it is not possible to establish the exact proportion of the population of modeled human receptors to be protected by a regulation or environmental standard, it is nonetheless possible to base the standard upon a chosen percentile and thus increase transparency. The transparency is sorely lacking in USEPA's Regional Screening Level Tables (RSLT) that are used by many as cleanup standards.[188] The choice of a percentile or proportion of modeled human receptors to be protected is a task of the sovereign, and the authority to choose a percentile should represent the will of the governed.

Numerical estimates of the percentile of protection.

To obtain such a quantitative estimate, the risk equation can be simplified as follows:

$$Risk = Concentration \times Exposure \times Toxicity \quad (1)$$

One can choose a target risk level such as one in a million and rearrange this equation to solve for concentration as a media standard to obtain:

$$Concentration = \frac{Target\ Risk}{Exposure \times Toxicity} \quad (2)$$

Because the target risk is a point estimate and a regulatory choice, the level of conservatism only depends on two factors – exposure and toxicity. Many risk analysts have developed probability distributions for exposure metrics and toxicity criteria. These can be used in Monte Carlo simulation to provide a distribution of risks in a hypothetical target population or to provide percentiles of exposure and toxicity. Multiplication of the percentiles of conservatism for each factor will give an estimate of the overall conservatism. Hence, if one assumes that the value chosen for exposure represents the 90th percentile and that chosen for toxicity represents the 90th percentile, then

$$P_{\text{Conservatism}} = 1 - (1 - 0.90) \times (1 - 0.90) = 99\% \quad (3)$$

It is important to remember that uncertainty increases greatly at very high or very low percentiles; hence, it would not be advisable to choose a percentile greater than the 99th as the proportion of a target population to be protected.[181]

Once an overall percentile of conservatism is chosen, the choice of an exposure percentile would limit the choice of the toxicity percentile. If the toxicity criterion is more conservative, then exposure will be less conservative to obtain the chosen overall percentile of conservatism. Alternatively, if the toxicity criterion is less conservative, then exposure will be more conservative. Monte Carlo simulation also provides a means of estimating a chosen percentile of risk.

An example using benzene

Here, information from USEPA and Monte Carlo simulation are used to determine the level of conservatism in the residential screening level for benzene in air from USEPA's Regional Screening Level Table (RSLT).[188] Values for both cancer and non-cancer effects were examined. The example below considers quantitative estimates of variability in exposure factors and quantitative estimates of uncertainty in toxicity criteria. Benzene was chosen because both the cancer and non-cancer toxicity criteria are based on human epidemiological data, thus avoiding the uncertainty associated with animal-to-human extrapolation.

However, there are other sources of uncertainty that cannot be quantified. First, both the cancer slope factor and non-cancer reference concentration are based on epidemiologic studies and the estimate of dose is uncertain. Second, the non-cancer risk assessment was based on a worker cohort that contained 44 Chinese men and the cancer risk assessment was based on the Pliofilm cohort of 577 US workers. These are both relatively small populations. Both the cancer and non-cancer assessments were conducted on occupationally exposed individuals and may not be applicable to the very young or very old. These worker cohorts consisted of mostly adult males, either Asian or Caucasian, and thus, differences in race, age or gender cannot be taken into account. Other sources of uncertainty may also exist.

The assessment for carcinogenic effects of benzene is presented in the Integrated Risk Information System (IRIS) online database and Support Document for benzene.[189] The range of inhalation unit risk (IUR) values for an air concentration of 1 $\mu g/m^3$ is from 2.2E-06 to 7.8E-06.[190] These values were assumed to be the 5th and 95th percentiles of a lognormal distribution.

The equation for the cancer-based RSL for ambient air was obtained from the Risk Assessment Information System website (RAIS, http://rais.ornl.gov/). This equation is:

Table 1. Distributions and Point Estimates for Exposure Factors used in the Example with Benzene

Exposure Factor	Abbr.	Point Estimate	Probability Distribution	Source
Residential Exposure Duration	ED_{res}	30 yr	Weibull (shape = 1.24; scale = 13.7)	Johnson and Capel (1992), cited in USEPA's Exposure Factors Handbook
Residential Exposure Frequency	EF_{res}	350 d/yr	Uniform(100, 365)	Professional Judgement
Residential Exposure Time	ET_{res}	24 hr/d	Uniform(8,24)	Professional Judgement

$$PRG_{res-air-nc}\left(\frac{\mu g}{m^3}\right) = \frac{TR \times AT_{cancer}}{EF_{res} \times ED_{res} \times ET_{res} \times IUR\left(\mu g/m^3\right)^{-1}} \quad (4)$$

where TR: target risk level quotient (unitless), ED_{res}: residential exposure duration (years), EF_{res}: residential exposure frequency (days/year), ET_{res}: residential exposure time (hours per day), IUR: inhalation unit risk $(\mu g/m^3)^{-1}$, AT_cancer: averaging time for cancer effects (25550 days).

Using the exposure assumptions in Table 1 and equations 3 and 4 and the distribution for the IUR described above, Monte Carlo simulation was used to develop a distribution of the cancer-based RSL. The residential RSL for air from the RSLT is 0.31 $\mu g/m^3$. This value falls at the 67th percentile of the RSL distribution. The 1st percentile of the RSL distribution would be protective of 99% of a hypothetical population at a one-in-a-million risk level and would correspond to a value of 0.023 $\mu g/m^3$, two orders of magnitude lower than the USEPA's RSL value. Hence, about one-third of a hypothetical population exposed to benzene at the RSL of 0.31 $\mu g/m^3$ would experience a risk greater than the regulatory target of one in a million.

Regarding the non-cancer effects of benzene, the RfD for benzene is based on a human occupational inhalation study.[191] The derivation is presented in the *Toxicological Review for Benzene*.[192] The data presented were the benchmark concentration (BMC) value of 13.7 ppm (15.6 mg/m^3, adjusted for continuous exposure) and the lower confidence limit (BMCL) value of 7.2 ppm (8.2 mg/m^3, adjusted for continuous exposure). The simple linear dose response model used absolute lymphocyte count (ALC) as the critical effect because it was the most sensitive hematologic effect in the study. With the same dose-response data and calculation methods used by USEPA,[192] an upper confidence limit (BMCU) of 53.6 ppm (61.1 mg/m^3, adjusted for continuous exposure) was obtained. The uncertainty in the BMC was represented by a lognormal distribution using the BMCL and BMCU as the 5th and 95th percentiles, respectively.

The choice of UFs was also presented.[192] Standard distributions for UFs are based on a lognormal distribution with a geometric mean of 3 and a 95th percentile value of 10.[69,70] When the distribution developed from the BMCL and BMCU values was divided by the UF distributions, the resulting distribution for the reference concentration was well fit by a lognormal distribution with a geometric mean of 0.65 mg/m^3 and a geometric standard deviation of 2.80.

The equation for the non-cancer RSL for ambient air was obtained from the RAIS website. This equation is:

$$PRG_{res-air-nc}\left(\frac{mg}{m^3}\right) = \frac{THQ \times ED_{res} \times \frac{365\,days}{year} \times \frac{1000\,\mu g}{mg}}{EF_{res} \times ED_{res} \times ET_{res} \times \frac{1}{RfC\left(mg/m^3\right)}} \quad (5)$$

where THQ: target hazard quotient (unitless), ED_{res}: residential exposure duration (years), EF_{res}: residential exposure frequency (days/year), ET_{res}: residential exposure time (hours per day), RfC: reference concentration (mg/m^3).

The resulting distribution for the RSL based on the non-cancer effects of benzene could be fit to a lognormal distribution with a geometric mean of 1.68 mg/m^3 and a geometric standard deviation of 3.10. The non-cancer RSL value from the online calculator at the RAIS website is 31.3 $\mu g/m^3$. This value occurs at the 0.08 percentile of the RSL distribution. The first percentile of the RSL distribution is 120.7 $\mu g/m^3$, a value four-fold greater than that developed using USEPA methods and defaults. Hence, only a very tiny fraction

of a hypothetical population exposed to benzene at the non-cancer RSL level of 31.3 $\mu g/m^3$ would actually experience the potential for non-cancer health effects.

The example with benzene illustrates (1) the potential for compounding of conservatism; (2) the lack of transparency in the RSLs and risk assessment methods used by USEPA and (3) the potential variation and disparity in the percentile of the population protected by the current RSL values.

Why the 99th percentile is an appropriate level of conservatism

The 99th percentile is a defensible choice for the overall level of conservatism. If one assumes that the 90th percentile values were chosen for both exposure and toxicity, the resulting environmental standard will be at the 99th percentile. The 99th percentile also has three advantages: (1) it is the highest level of protection with reasonable levels of uncertainty; (2) the values of standards obtained using the 99th percentile are similar in magnitude to existing standards and (3) the choice of the 99th percentile is defensible to the regulated community because of the increased transparency and to the public because of the high level of protection it affords.

The choice of the 99th percentile is also consistent with both deontological and teleological ethics. The choice of the 99th percentile is an expression of deontological ethics viewed as likely protecting an even higher percentile of the target population because the likelihood of a highly susceptible individual who is also highly exposed becomes very small in a large population. With regard to teleological ethics, the 99th percentile can be viewed as an attempt to include the best available scientific information on human variability in both exposure and toxicity and protecting individuals who are both highly exposed and highly susceptible.

Achieving a reasonable level of uncertainty and a consistent approach are two additional compelling reasons for choosing the 99th percentile. In addition, the act of choosing a percentile represents a degree of transparency that presents the opportunity to alter this percentile, either higher or lower, based on data on human behavior that bears on the exposure assessment or data on human susceptibility that bears on the toxicity criterion.

Conclusions

The science underlying risk assessment continues to advance. Regulatory personnel should not only stay abreast of these advances but also remain aware of the pitfall of confusing the ethics of intention with the ethics of the consequence. Whatever the current state of knowledge might be, there will be those who fall back on the precautionary principle, claiming the state of knowledge cannot meet the challenges posed by the exigencies of regulation.

It behooves those in the risk assessment field to understand the ethical nature of their activity and to change their perspective as new science emerges. Given the emphasis on consistency[193] and the glacial pace with which change occurs in regulatory risk assessment at USEPA, one cannot help but think that risk assessment practitioners in the late twenty-first century, fifty to one hundred years hence, will characterize today's regulatory personnel as Luddites, much as we think of the nay-sayers who protested the building of the Liverpool-Manchester railroad in 1825.[17]

> ... 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.

In the fullness of time, how will history judge USEPA risk assessors and toxicologists with regard to their open-mindedness and acceptance of new science? As a society, we cannot turn back the clock, no matter how much we might long for a simpler and less complex time. Science and technology have changed the world in both large and small ways. Risk assessment is a means of apportioning the burden of the technology we all enjoy in a democratic manner.[12]

Regulatory personnel should remain aware of the pitfall of confusing the ethics of intention with the ethics of the consequence vis-à-vis environmental regulation. Although a number of programs at other environmental regulatory agencies have suggested an exposure percentile to use in a standard, these other agencies have been uniformly silent about the choice of an overall level of conservatism. The 99th percentile is a reasonable choice for the overall level of conservatism because:

- The 99th percentile affords a high level of protection with reasonable levels of uncertainty; and
- The choice of the 99th percentile is defensible both to the potentially exposed public because of the high level of protection and also to the regulated parties because of its transparency.

In addition, the increased level of transparency associated with the choice of a proportion of the target population to include in an environmental standard fosters flexibility – a higher or lower percentile may be chosen on a case-by-case basis if information suggests that such a choice is warranted. This flexibility will lead to more responsive environmental regulation that balances protection of public health and the stewardship of societal resources.

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