BELLE NEWSLETTER

Biological Effects of Low Level Exposures

A Publication of the Northeast Regional Environmental Public Health Center, University of Massachusetts, School of Public Health, Amherst, MA 01003
Vol. 13 No. 1, July 2005, ISSN 1092-4736

WHAT IS THE PURPOSE OF A RISK ASSESSMENT?

This is a basic question and one that governs what constitutes the risk assessment process and what types of data are used. In a recent document entitled "AN EXAMINATION OF EPA RISK ASSESSMENT PRINCIPLES AND PRACTICES", A Staff Paper Prepared for the US EPA by Members of the Risk Assessment Task Force (EPA/100/B/001) March, 2004 the purpose of a risk assessment was defined in the quoted paragraphs below. Of particular interest to BELLE is the conclusion that effects that could be beneficial may not be mentioned in the risk assessment process. As the BELLE readership is well aware, BELLE has devoted considerable effort to clarifying the nature of the dose response in the low dose zone. These efforts have revealed that the hormetic dose response is common in the toxicological literature when studies are designed to assess below NOAEL responses. Many of these studies indicate that below traditional NOAEL doses reduce background disease incidence, yielding what many would call a beneficial effect. In fact, a number of recently published studies indicate that the hormetic dose response, when properly studied, is more common than other dose response models such as the threshold model (Calabrese and Baldwin, 2001, 2003). Thus, it is believed that the statement of the EPA staff paper needs to be explored, discussed and evaluated by risk assessment scientists outside of the Agency.

Consequently, I invited a number of recognized experts in the field of risk assessment that are independent of EPA for their evaluation of what EPA considers to be the "purpose of a risk assessment". Immediately below is the EPA statement that the experts were invited to respond to. The expert responses comprise the remainder of this newsletter.

Quotation From U.S. EPA Document:

Section 4.1.3 (page 53) - ***Does Any Change Seen in Animals Indicate There Will Be a Problem for Humans?***

> *"It is generally accepted that there can be numerous changes to the recipient organism (the animal under study) following exposure to a chemical, some of which may be beneficial, adaptive, early manifestations on a continuum to toxicity, overtly toxic, or several of these things in combination. Unless there are data to indicate otherwise, a change that is considered adverse (i.e., associated with toxicity) is assumed to indicate a problem for humans.*
>
> *It is recognized that a diversity of opinion exists regarding what is "adverse" versus "adaptive," both within EPA and in the general scientific community. At present, there is no Agency-wide guidance from which all health assessors can draw when making a judgment about adversity. Therefore, various experts may have differing opinions on what constitutes an adverse effect for some changes.*
>
> *Moreover,* ***as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned*** *(Bold-emphasis added).*

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NONLINEARITY IN BIOLOGY, TOXICOLOGY AND MEDICINE JOURNAL

Starting January 2005 the journal **NON-LINEARITY: Biology, Toxicology and Medicine (www.nonlinearity.net)**, now entering its third year, will be editorially directed by BELLE, published and owned by the University of Massachusetts/Amherst. The consolidation of all journal activities under the auspices of BELLE is designed to enhance both the visibility and leadership role of BELLE in the area of low dose biological effects as well as to facilitate an improved promotion of the journal and a more direct interaction amongst contributing authors, BELLE and the scientific community.
NONLINEARITY in Biology, Toxicology and Medicine has an internationally recognized editorial board, a strong peer-review process, with all final manuscript decisions on publication made by Associate Editors with recognized excellence in their respective areas. A listing of the papers published in NONLINEARITY: Biology, Toxicology and Medicine over the past two years can be found on the journal website. We invite you to subscribe to the journal as well as becoming a contributor via the submission of relevance manuscripts. To subscribe to the journal please visit the journal website (www.nonlinearity.net) and follow the directions for subscription.

INTERNATIONAL HORMESIS SOCIETY

GOAL

A growing number of scientists, including toxicologists, pharmacologists, biostatisticians, epidemiologists, occupational and environmental medical researchers and others have begun to display considerable interest in the topic of hormesis, a dose response phenomenon characterized by a low dose stimulation and a high dose inhibition. While there are many professional societies that have a general interest in dose response relationships, none explicitly is devoted to the topic of understanding the nature of the dose response in general and hormesis in particular. The diversity of professional societies that may consider dose response issues, including hormesis, is nonetheless quite broad ranging from the agricultural to the biomedical and clinical sciences. However, nearly without exception, these societies tend to be strongly organized around professional advancement and not focused on specific scientific concepts. This makes the issue of hormesis one of diffuse interest across a broad range of professions. The present situation represents a major obstacle for the integrated assessment of the dose response in general and hormesis in particular. In order to provide intellectual and research leadership on the topic of hormesis, a new professional association has been created called the International Hormesis Society (IHS).

The Society will be dedicated to the enhancement, exchange and dissemination of ongoing global research efforts in the field of hormesis. In addition, the Society will also strongly encourage the assessment of the implications of hormesis for such diverse fields as toxicology, risk assessment, risk communication, medicine, numerous areas of biomedical research, and all other biological disciplines including relevant engineering domains dealing with the dose response.

LOCATION

The International Hormesis Society will be administered by BELLE, School of Public Health & Health Sciences at the University of Massachusetts at Amherst.

MEMBERSHIP

The IHS is a professional society designed to enhance understanding of the nature of the dose response and its implications for science and society. Those individuals with a professional interest in these areas will be eligible for membership. Applicants for membership must complete the attached membership application form. Corporate memberships would be $1000.00 (U.S.) per year while Individual membership dues will be $125.00 (U.S.) per year. Student memberships are encouraged with an annual dues set at $10.00. Applications should be mailed to the **BELLE Office, Environmental Health Sciences Program, Morrill I, Room N344, University of Massachusetts, Amherst, MA, 01003.**

As part of IHS membership, each corporate and individual member will receive a subscription to the journal **Nonlinearity in Biology, Toxicology and Medicine**, which is a peer-reviewed quarterly journal. In addition, there will be a Society Newsletter developed for the membership. There will also be an annual conference to which all society members will receive a reduction in registration fees.

INTERNATIONAL HORMESIS SOCIETY

Application for Membership

Application for the following membership category (mark only one):

Corporate Membership	☐	$1,000.00/year
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University of Massachusetts
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Fax: 413-545-4692
E-mail: belle@schoolph.umass.edu

Signature of Applicant **Date**

AN EVALUATION OF THE EPA DEFINITION OF A RISK ASSESSMENT

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The US Environmental Protection Agency (EPA) recently published a Staff Paper, "An Examination of EPA Risk Assessment Principles and Practices" (US EPA, 2004). A key purpose of the paper was to describe current EPA risk assessment principles and practices, and to identify ways to strengthen risk assessment practices at EPA. As part of this analysis, EPA evaluated how the agency should consider effects that may be, "...beneficial, adaptive, early manifestation on a continuum to toxicity, overtly toxic, or several of these things in combination." EPA concluded that because there was no agency-wide guidance regarding adversity of effects, that such considerations could not be considered in a risk assessment. Specifically, the agency stated, "…effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned."

This guidance is troublesome. Not allowing risk assessors even to *mention* "effects that appear to be adaptive, non-adverse, or beneficial" is inconsistent with general principles of scientific analysis in which a complete and unbiased presentation of information is essential. Risk assessors frequently consider these types of effects as part of a complete analysis. Moreover, the guidance appears to be inconsistent with EPA's adoption of the OMB guidelines regarding the quality of scientific information to be used by federal agencies in the context of analysis and decision-making (USOMB, 2002). For example, the OMB guidelines state that information needs to be "objective, realistic, and scientifically balanced" (USOMB, 2002).

While one might construe the motivation for this guidance as an effort to avoid implying that any detectable physiological change is to be avoided (a laudable goal), such avoidance is likely to be counter-productive. Specifically, the Staff Paper recommendation could result in unexpected (and unfortunate) impacts, discouraging use of mechanistic information, and could potentially have detrimental impacts to public health. In the interest of fuller risk characterizations and ensuring that risk managers have all relevant information, we strongly encourage EPA to reconsider this guidance. More detail on the basis for these conclusions is provided in subsequent paragraphs.

1. Risk assessors frequently distinguish between adverse and non-adverse effects and incorporate such distinctions into their analyses. For example, in 2000, the American Thoracic Society updated their 1985 definition of an adverse respiratory health effect with respect to air pollution (ATS, 1985; ATS, 2000). The ATS guidance (1985; 2000) recognizes the important need for risk management decision-making to specify which types of health effects are considered adverse. ATS also recognized how minimal changes in levels of biomarkers may reflect a homeostatic response, and that biomarker levels are reflective of injury only when levels exceed certain thresholds. With respect to pulmonary function tests, a small transient loss of lung function (*e.g.,* a decrement of 10% or less in FEV_1) would not be automatically considered adverse; however, a reversible decrement of lung function in the presence of symptoms would be considered adverse. US EPA Staff Papers on air pollutants have used this guidance in conducting population-based descriptions of risk; for example, in the Office of Air Quality Planning and Standards Staff Paper (USEPA, 1996), US EPA considered decrements in lung spirometry of 3% to ≤ 10% that last less than four hours to be non- adverse.

2. Scientists frequently analyze biochemical or cellular responses associated with chemical exposure in the context of homeostatic mechanisms and identification of adverse (and non-adverse or adaptive) responses. Such considerations are critical to the appropriate use of animal data for purposes of predicting human risk. For example, the rat thyroid is, for a number of reasons including serum half-life of thyroid hormone and available thyroglobulin colloid precursor for thyroid hormone, more susceptible than the human thyroid to perturbations in the presence of thyroid active agents, such as perchlorate (as reviewed in Lewandowski *et al*, 2004). Thus, the rat exhibits decreases in serum thyroid hormone levels at fairly low perchlorate exposure levels (*e.g.* T3 and T4 decrease at 0.01 mg/kg/d with subchronic exposure) that are readily reversible once exposure ceases (Siglin, *et al*, 2000); however, the rat does not exhibit evidence of abnormal thyroid histopathology (effects that would potentially be considered adverse) until much higher levels (10 mg/kg/d). In contrast, the human, because of greater thyroglobulin reserves and longer-lived thyroid hormones, has a much more robust homeostatic mechanism, showing no effects on thyroid hormone levels at subchronic perchlorate doses of approximately 0.5 mg/kg/d (as reviewed in

Lewandowski *et al*, 2004). In this example, failing to consider the adaptive and non-adverse nature of the T3, T4 changes in the rat with respect to thyroid hormone synthesis at low levels of perchlorate exposure would result in inappropriately high estimates of risk for humans potentially exposed to perchlorate.

3. The world of "omics" is providing scientists with vast amounts of new information on changes in gene transcription, protein synthesis, post-tranlational modification, and metabolism as a consequence of chemical exposure. It is essential to evaluate the significance of such changes, *e.g.,* pre-clinical, adverse, adaptive, in order to help realize the potential of these important new tools. For example, Xie and coworkers (2004) looked at changes in gene expression in livers of mice exposed *via* ingestion to inorganic arsenic or organoarsenicals along with 12-0- tetraacanoyl phorbol-B-acetate (TPA) applied to the skin. Seventy of the 600 genes examined displayed increased or decreased expression. It is likely that some of these changes are causally related to the toxicity of arsenic, others may be a secondary to arsenic toxicity, and yet others may reflect general responses to toxicological insults. In this study, the investigators proposed certain genes as potentially being relevant to carcinogenicity. Scientists must be encouraged to evaluate the toxicological relevance of these changes in gene transcription as a consequence of toxicant exposure and to discriminate between adverse, non-adverse, and adaptive effects that may mitigate toxicity. At the very least, risk managers must be informed regarding the potential health significance of such changes.

4. Preventing risk assessors from considering potentially beneficial responses of chemical exposure eliminates consideration of hormesis[1]. Yet, hormesis as a consequence of chemical exposure does not appear to be an uncommon phenomenon, or one without significant scientific support. A comprehensive analysis of 668 dose-response relationships meeting pre-defined criteria for inclusion indicated that that 245 (37% of 668) dose-response relationships demonstrated a hormetic response (Calabrese and Baldwin, 2003). Failure to consider hormesis in risk assessment means that the public health impact of reductions in exposures may be partially described, and possibly for a significant fraction of chemicals. This is not to say that the scientific evidence for and implications of hormesis can readily be applied to human health risk assessment. After all, most of the evidence presented by Calabrese and Baldwin (2003) is from non-mammalian species, and a number of important uncertainties exist with respect to incorporation of hormesis into risk assessment. These include potential differences in hormetic zones among strains of animals and between humans, the relatively modest magnitude of the improvement in the parameter being measured and the difficulty in relating some of the parameters measured to clinically relevant health effects. Yet, the toxicological significance of hormesis has broad-reaching implications, *e.g.,* development of RfDs or identifying dose-response models for carcinogenic risk assessment; thus failing to even qualitatively consider hormetic responses, where evidence exists for the chemical being studied, surely does a disservice to the field of risk assessment and potentially provides a biased perspective on risk to risk managers.

NOTES

1 Defined as "...a dose-response relationship in which there is a stimulatory response at low doses, but an inhibitory response at high doses, resulting in a U- or inverted U-shaped dose response".

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SHOULD APPARENTLY BENEFICIAL EFFECTS OF LOW DOSE EXPOSURES TO AGENTS BE INTEGRATED INTO RISK ASSESSMENTS PERFORMED BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY?

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INTRODUCTION

Simply put, risk is the chance that an adverse event may occur. Perhaps the most frightening risks to the general population are those that involve adverse health effects caused by the actions taken by someone else without the affected person's consent. Many of today's major litigations involve the exposure of unwitting or non-consenting persons to (often undetectable) noxious agent(s) that may adversely affect their health or the environment resulting from the actions of a responsible party that is often an industrial or business entity. Indeed, it was in response to growing public awareness of the health and environmental consequences of pollution (as articulated by such authors as Rachel Carson, 1962) that the United States Environmental Protection Agency (USEPA) was formed in 1970. During the ensuing three decades, the methodology for determining whether humans are in jeopardy from exposure to environmental contaminants has evolved to the point where it has become quantitative. These quantitative procedures have been codified in various government guidance documents (e.g. USEPA, 1984, 1986, 1991, 1994, 1996, 2000). To assure that risk assessments are performed in a uniform manner, the specific factors that may and may not be considered have been established. A recent staff paper prepared for the USEPA by the Risk Assessment Task Force reflects this restriction of the methodology in that "effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned [in a risk assessment]" (USEPA, 2004). The purpose of the present paper is to consider the issue of what the types of input that are, or should be, incorporated into risk assessments performed by the USEPA. Specifically, we will briefly address advantages, challenges, and means for considering potential benefits when assessing risk.

RISK ASSESSMENT AND SAFETY

Safety is commonly defined as "an acceptable level of risk" (e.g., Rowe, 1977). Because the tolerance of different individuals for risk is subjective, varies greatly, and is difficult to communicate clearly, a set of procedures has been developed to help objectify and quantify risks. These procedures grew out of the methods used to develop actuarial tables by insurance companies to determine the likelihood and extent of losses and the need of adjudicators in the legal system to make decisions based on factors with varying degrees of uncertainty (Suter, 1993; Whitney, 1976; Black, 1988; Carnegie Commission, 1993; Faigman et al., 2002). The currently used, overarching paradigm for risk assessment was articulated and refined in the National Research Council's monographs on risk assessment (1983; 1994). Various federal agencies have interpreted the paradigm to develop principles and assumptions that are crucial to regulating exposures of the public to those risks for which each agency is responsible. Roberts and Abernathy (1996) provide a detailed and thoughtful treatment of risk assessment methods used by USEPA. They are careful to define risk as the possibility of being exposed to a hazard, and risk assessment as the likelihood of adverse consequences from an estimated exposure to the identified hazard. Following from their definition of risk, possible benefits would not be considered in risk assessment.

ENVIRONMENTAL PROTECTION AGENCY

The statutory and legal underpinnings for the risk assessment of chemical and physical agents by the USEPA are found in a diverse set of statutes that lay out the context, scope, and input to regulatory decision making. Each statute pertains to a particular kind of agent (e.g., pesticide) or route of exposure/environmental medium (e.g., air, water) and defines the basis for

determining risk (e.g., solely on risk to health or environment; consideration of technology-based standards; balancing of risks, benefits, and costs) leading to a multiplicity of standards (GAO, 2001). Additionally, to foster a cohesive approach towards risk assessment, the USEPA has published in the *Federal Register* numerous guidance documents related to various toxicological disciplines (see review by GAO, 2001). Because the Agency is sensitive to the constraints placed on the various Program Offices, its guidance documents have concentrated on the commonality among those Program Offices that are responsible for risk assessments, and will therefore consider only adverse health and/or environmental effects. This does not mean that USEPA is blind to the existence of competing considerations about acceptability of risk; rather it means that these additional considerations must be dealt with on a Program-by-Program basis as part of the risk management process (National Research Council, 1983; Roberts and Abernathy, 1996). Thus, the Agency may be cognizant of possible impacts of beneficial effects on the regulation of a substance, but prior to considering these impacts, a risk assessment is performed without this information in an attempt to make the risk assessment process as objective and consistent as possible. Additionally, USEPA and other agencies have attempted to make the process quantitative. A major endeavor in the process is the statement of the relationships among extant data in a readily and transparently manipulated numerical form. This requires an understanding of the dose-response relationship, including its limitations.

THE DOSE-RESPONSE RELATIONSHIP

One of the fundamental principles underlying the assessment of toxicity is the dose-response relationship which assumes that the there is a causal connection between exposure to a given agent and the resultant adverse effect (Klaassen and Doull, 1980). When depicted graphically by plotting the effect (or responses) as the dependent variable and the independent variable as the logarithm of dose, the resulting graph is a sigmoidal curve (Bliss, 1935). This relationship approaches linearity throughout the middle of the measurable dose range, but deviates dramatically at the extremes of very high and very low doses. When the data are re-plotted using probit units on the ordinate (instead of percentage of affected organisms), the resultant graph is linear over much of its extent (Litchfield and Wilcoxon, 1949). Extrapolating the plot below the lowest dose studied (if a non-zero effect was measured at the lowest dose) is very difficult because the behavior of the elicited response at very low doses is largely unstudied (Munro and Krewski, 1981; Paustenbach, 1989) although it will likely deviate from linearity in an unpredictable fashion (Borgert et al., 2004).

Concept of Threshold

The highest exposure level that produces no adverse effect is the threshold. The threshold marks the upper bound of safe exposure levels in the exposed experimental organism. For those adverse effects that are quantal, such as death or the presence/absence of a specific condition, the no observed [adverse] effect level (NO[A]EL) is an estimate of the threshold dose for adverse effects that is determined empirically in animal studies. In combination with uncertainty and/or modifying factors (often divisors of 10), the NO[A]EL is used to establish exposure levels that are considered to be safe for people. The ability to detect rare adverse events (or an adverse outcome in extremely sensitive individuals) is, however, largely determined by the number of subjects under study. For cases where the adverse effect in question is continuous (e.g., loss of body weight, increased weight of the liver) or where a single molecule of the agent in question could initiate a series of deleterious events (e.g., unrepaired DNA damage that can lead to tumor formation) knowledge of the behavior of the dose-response relationship at doses lower than those typically measured in safety assessments, which are used to construct the dose-response curves, might be needed.

Nature of the Dose-Response at Low Levels of Exposure

The toxic effects of agents can be predicted with greatest confidence when the exposure levels fall within the range of those used to construct the dose-response curve; behavior that falls outside of the range of measured doses must be extrapolated and is subject to uncertainty. Recall that mathematical transformations of the data were required to make the dose-response curve linear throughout its measured regions and that the deviations occurred especially at the low end of the curve. By and large, there are few toxicological data for substances tested at doses below the NOAEL. Risk assessors must assume that the behavior of the dose-response curve either maintains its linear nature or that it deviates in some defined way as the exposure level decreases to zero. A variety of curves are possible (Munro and Krewski, 1980; Paustenbach, 1989), including a straight line extrapolation of the dose-response curve, either following its original slope until it reaches the x-axis or by extrapolating form the last measured point to the origin. Alternatively, the curve may deviate from linearity at low doses either appearing more toxic, less toxic, or, for the purposes of our present discussion, changing its contour to indicate a positive effect resulting in a "j-shaped" dose-response curve. The latter case is the condition of hormesis, the existence of which has been the subject of recent study (Calabrese and Baldwin, 2001; 2003).

Potential Consideration of Benefits

If a benefit is considered to be an advantage or favorable circumstance, it may be either related or unrelated to

the specific toxicologic mechanism of action of the agent. In the latter case (unrelated to mechanism of action), it will be difficult to include such information in a quantitative risk assessment because there is likely to be no representation of the advantage in the dose-response curve modeling a specific response or other toxicity information. An example of a benefit that is unrelated to the toxicologic mechanism of action could be that of selenium. In microgram quantities, selenium is incorporated into glutathione peroxidase, which benefits the body by helping to control cytosolic free radicals, and it aids in regulating the reduction status of ascorbic acid, whereas at higher intakes selenium exerts toxic effects by several means including interference with protein synthesis and aberrant transsulfuration metabolism (European Commission, 2000). In the former case (related to mechanism of action), however, the interaction should be modeled because it will be represented on the dose-response curve. In the event that the benefit occurs at low doses, it should be reflected by a change in the shape of the dose-response curve and therefore would be considered as part of the risk assessment. In some cases, low doses of two chemicals that share a common mode of toxicologic action can interact in a manner that *decreases* their net toxicity, as in the case of hydrogen cyanide and hydrogen sulfide (Borgert et al, 2004). Should cases exist where one suspects that beneficial effects may be observed at lower exposures than those tested, additional testing could be performed (underwritten by responsible parties) and the data could be submitted to the USEPA for review.

CONCLUSIONS

The implications for risk assessment of a hormetic dose-response can be far reaching and are discussed in a theoretical context by Calabrese (1995). From the standpoint that the change in the dose-response curve is caused by exposure to the agent of concern, it seems logical that any benefit that is derived from low-level exposure is fundamental to the interaction of the agent with the exposed organism and should be considered in the risk assessment of the agent when such a response is known to occur. The existence of a *bona fide* beneficial effect of low dose exposures to a given agent should be considered when assigning uncertainty factors in the calculation of safe exposure levels. If such data are expected or suspected to exist, they should be generated and submitted to the USEPA by interested parties for incorporation into risk assessments. In the absence of a demonstrated hormetic effect of low-dose exposures, however, the current methods used by USEPA are adequate for protecting human health and the environment, provided that they remain flexible enough to accommodate new, reproducible data that may alter our understanding of the effects of agents, whether they be toxic or beneficial.

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THE ISSUE OF RISK IN COMPLEX ADAPTIVE SYSTEMS: THE CASE OF LOW-DOSE RADIATION INDUCED CANCER

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ABSTRACT

Living systems exist in hierarchical levels of biological organization, ascending from the basic atomic-molecular level, to the cellular level, the tissue-organ level, and the whole organism. All levels and elements at each level communicate with each other though intricate intra- and intercellular signaling through many specified molecular interactions. These regulate homeostasis between the system levels and their individual elements.

The probability of a defined effect at the basic atomic-molecular level per impact increment of a toxic agent such as ionizing radiation at that level appears constant at low doses, even if the probability constant may change as a consequence of a previous exposure. Thus, at a given state of the system, the incidence of effect at the atomic-molecular level increases linearly with the number of impact increments in terms of energy deposition events. Primary effects may amplify to damage and there are immediate attempts at repair of damage from an effect.

Amplification and propagation of damage at, and from, the basic to higher levels of biological organization meets resistance, the degree of which per impact increment is not constant. It changes with the number of impact increments. This resistance encompasses both physico-chemical and biochemical reactions. The corresponding biochemical reactions express the physiological system's capacity to respond to perturbations of homeostasis at and between the various levels. Types and degrees of these responses depend on the system and the degree of homeostatic perturbation. At relatively mild to moderate degrees of perturbation, protective responses appear with a delay of hours and may last for months, shield also against endogenous non-radiogenic damage, and in doing so may prevail over radiogenic damage. With increasing degrees of homeostatic perturbation damage eventually overwhelms adaptive protection. Thus, systems do not respond in a linear function of impact increments at the lowest level of biological organization.

For assessing probability of radiation damage per absorbed dose, i.e., risk, in complex adaptive systems, both damaging and protecting responses need attention, and to exclude one for the other is scientifically unjustified and misleading.

INTRODUCTION

The term risk is commonly used, yet often in a non-qualifying manner. Thus, risk colloquially appears to be synonymous with danger and one attaches varying degrees of danger or risk to an event that comes from an impact of a potentially detrimental object or agent on another object called target. This leads superficially to assume that risk or danger refers directly to the severity of damage rather than to the probability that certain damage occurs from a given degree of impact on the target. This is, of course, of greatest importance not only to insurance companies but also to public health and its administrators in their efforts to protect people from undue exposures to a great variety of toxic agents. Many threatening agents, such as cars in traffic, bullets from a gun, dust particles in the air, or microbes and chemicals in food, need consideration in various kinds of exposures or accidents, and risk of illness from such exposures or accidents need to be known for devising proper protection.

A special case appears to be the threat from exposure to ionizing radiation at various absorbed doses. There is a widely spread general notion that ionizing radiation poses a danger at any level of absorbed dose. This fear derives from the observations following the accidental irradiation of humans and, especially, from the study of the consequences of the atomic bomb explosions in Japan. The follow-up of the survivors of these explosions shows that cancer incidence in this population appears to rise linearly with absorbed dose over a certain dose range above about 0.1 - 0.2 Gy. The corresponding dose-risk relationship below that dose is under dispute. Various experimental and epidemiological observations over the past two decades, however, increasingly demonstrate that biological effects at doses below about 0.1 – 0.2 Gy cannot be predicted by assuming that the degree

of proportionality between dose and effects seen at higher doses also applies to low doses. The reason for this lack of constant proportionality between absorbed dose and biological effects at low doses, at first sight, is difficult to comprehend. Yet, a careful appreciation of the complexity of biological systems from microbes to man illuminates not only the apparent lack of a constant proportionality between absorbed dose and effect at low doses, but even benefit rather than damage. The reason for the particular effects of low doses lies in the hierarchical structure and function of biological systems extending from the atomic-molecular level, to the cellular level, the tissue-organ level, and to the whole organism, and all levels functionally interact through intricate intra- and intercellular signaling. The targets of ionizing radiation in biological systems are atoms within molecules, and biological radiation effects of any kind are triggered at the atomic-molecular level of biological organization. In order to cause health effects the damage at the basic level of organization needs to propagate to the cellular, tissue-organ level and eventually to the entire organism, where these effects may come to bear. The present discourse shortly addresses principal issues regarding risk of detriment following low-dose exposures to mammals and man with the view that biological systems operate in complex structures and function adaptively **[1].**

THE MEANING OF RISK

Irrespective of the type of encounter between two mass objects, damage to one of the objects, here called target, may arise under certain conditions. Thus, a moving object may collide with a resting target, or vice versa. Object and target may be of quite different kinds. Regarding human health, for instance, one may consider a moving car hitting people, or a bullet from a gun injuring an individual, or a microbe invading a cell, or ionizing radiation interacting with an atom in a molecule crucial to life. Extent of damage to a target occurring from an impact only rarely increases linearly with the degree of an impact. Obviously and empirically, the intensity of an impact on a target does not necessarily correlate with the degree of damage. An example may be the encounter between a potentially detrimental object such as a chisel and a target object such a piece of wood. In this case, a cut of a certain depth, i.e., a groove, in this piece of wood only comes from a certain force on the chisel. There will be no groove at all, if the force on the chisel remains below a certain value. On the other hand, if the force on the chisel reaches a certain high value, the piece of wood will be cut fully. Any further increase of the force will do no more than fully cut the wood. In fact, when any such type of encounter of an object on a target is under careful observation using sensitive methods of measurements, there appears to be a threshold of degree of impact of a potentially detrimental object on a target before a defined effect arises and above a high value of force there will be no further increase of the effect. In principal, the relationship between degree of impact and extent of effect shows a sigmoid function with often a threshold for causing the effect.

The degree of effect from an impact on a target should not be confused with risk. The latter expresses the probability of a certain effect to arise from a given impact on a particular target. In order to measure risk, one needs to repeat many times an impact of certain intensity and observe the frequency of a certain effect from these impacts on targets of the same kind. The number of defined effects occurring from the number of certain impacts of equal intensities, here denoted as impact increments, gives the probability of that effect to occur on average per impact. This quotient expresses the average risk of a defined effect per impact increment and it is constant with a range of error under the given experimental conditions. If one adds up the results of an increasing number of such measurements in parallel, the number of impact increments, each one on a corresponding separate target, increases, and so does the number of defined effects. Here of course, the increase of the number of such effects is linear with the number of impact increments. Let targets of the same kind be bundled but independent of each other in one system, then one also states that the risk of the defined effect to appear in that system increases linearly with the multiple of given impact increments on the system containing these targets. Many different effects are, thus, amenable to assessment of their individual risk per impact increment.

RISK IN BIOLOGICAL SYSTEMS

This latter scenario finds application in biology, where, for instance, the amount of damage to the genetic material, the DNA, such as double strand breaks, DSB, is plotted against absorbed dose from ionizing radiation. The latter expresses absorbed energy per unit exposed mass, and this energy is delivered in multiple impact increments, called energy deposition events **[2]**. The number of DSB in irradiated DNA rises linearly with absorbed dose **[3].** Thus, the measurable probability of a DSB, per average energy deposition event of a given size, i.e. per unit absorbed dose, appears constant over a certain dose range. Over that dose range the DNA poses separate targets of the same kind in the same system with the average energy deposition events being defined impact increments.

One generally assumes that the extent of persisting DNA damage in a mammal with physiological DNA repair determines the probability of a malignant tumor in that mammal, and if DNA repair is defective, the cancer incidence rises accordingly **[4].** This assumption leads to plotting the risk of cancer to mammals as a linear

function of absorbed dose, from the lowest value of dose up over a certain dose range.

Origins of non-linearity

This straight forward approach to express risk of cancer as a linear function of absorbed dose, however, fails to take into consideration the complex structures of living systems, which function in hierarchical levels, as schematically shown **Fig. 1 [5]**. The basic atomic-molecular level, the cellular level, the tissue-organ level, and the whole organism all functionally interact through intricate intra- and intercellular signaling at and between these levels. This is illustrated in **Fig. 2**. At least three principal loops of signaling exist and each has many defined biochemical interactions: one within cells; one between cells at the tissue level; and one between cells of different tissues. All signals have their specific messengers in many different molecular forms and all finally provide the particular organism's responses **[6, 7].** The signaling loops at and in between the various levels operate to maintain competence of proper function through corresponding structures in a homeostatic balance **[8]**.

When the homeostatic balance at any level suffers perturbations, damage may result, and, in reverse, damage may cause perturbation. Perturbation and damage initiate some form of response depending on the degree of perturbation of homeostasis at that level **(see Fig. 2)**. Minimal perturbation are ineffective in causing a response. Mild to moderate perturbations at an organizational level trigger repair, if needed, and tend to result in types of system behavior which commonly define stress responses, whereas with increasing degrees of perturbation certain dissociations of structure and function bring amplification of damage, system failure, and eventually death, when the repair response is defective and/or overwhelmed. The relationship between degree of perturbation and system response expresses a sigmoid function.

The responses to mild to moderate perturbations at various levels of organization are characteristic of complex adaptive systems. They generally include a multitude of biochemical and cellular reactions, including changes of gene expression and in feedback control loops between molecules within cells, between cells in a tissue, and between cells of different tissues, i.e. at and between the organizational levels.

It is difficult to differentiate properly between a given perturbation of homeostasis and damage. Usually, one associates the latter in biology with a disruption of physiological function on the basis of structural alterations that require some type of repair before physiological function can resume. Damage may grow or amplify at a given level horizontally, and may ascend and propagate vertically into higher levels. Thus, damage of a certain degree at a lower level may cause a mild to moderate perturbation at the higher level and if this perturbation is strong enough it still may affect the next higher level. The development of an infectious disease within a normally functioning body with an appropriate immune system is a well know example and more is discussed below.

Damage amplification

Damage amplification occurs at the molecular and cellular level, for instance, following damage by ionizing radiation at the atomic-molecular level of organization. One such amplification expresses genomic instability, and the other bystander effects. The former amplifies damage restricted to the genome of a cell and, consequently, it affects the whole cell, which as smallest living unit reacts as a whole in response to alterations of its constituent elements. **[9, 10].** Genomic instability increases cellular vulnerability to mutagenic agents, and may persist throughout many cell generations, for example over repetitive transfers in cultures. Another well-known amplification of damage may affect a number of neighboring cells that did not suffer primary damage but become involved in terms of bystander effects **[11, 12]**. Thus, damage to DNA may arise in non-irradiated cells by way of bystander effects from irradiated cells and is considered a tissue effect. The generation of these damage amplification events in cells and tissue are still not fully understood, yet the probability of such damage amplification seems to increase to a plateau with increasing numbers of impact increments, i.e. energy deposition events. It is crucial to ask to what degree primary and amplified damage at the level of cells and tissue may ascend and propagate to result eventually in clinically apparent detriment.

Damage propagation from lower to higher organizational levels

Perturbations of homeostasis, of course, also occur between levels of biological organization, i.e., damage at a lower level may cause perturbation at the higher level. An obvious example becomes apparent when one follows the effects of ionizing radiation. As proven experimentally, the number of primary DSB in cells in an irradiated population increases as a linear function of absorbed dose, i.e. of multiples of impact increments, and at low doses bystander effects and genomic instability may amplify. The sum of this and other similar damage needs to propagate into the higher levels of organization, i.e., eventually to the tissue-organ level, before a clinically apparent detriment appears, for example a malignant tumor.

In principal, ascending propagation may on the one

hand again amplify damage and on the other extreme lead to damage reduction or disappearance. In normally functioning biological systems, the relative probabilities of the two outcomes add to determine the probability of a clinical detriment. Innumerable observations, as will be summarized below, ascertain the power of biological systems to resist the propagation of damage to increasingly higher levels of biological organizations; in other words, damage meets repetitive or "reparative" resistance of various kinds at subsequent levels. The degree of this resistance appears to depend on the extent of damage at the lower level.

One resistance at a given level of biological organization is simply a physico-chemical type of threshold against damage propagation from a lower to the next higher level, as the chisel meets on wood, as was mentioned above. Existing redundancies of structures at various organizational levels, such as of molecules, cells, and tissue-organs, need be overcome or broken to cause a damage from a lower level to perturb structure and function at the next higher level. The other resistance against damage propagation from lower to increasingly higher levels of biological organization is governed mainly by the responses to homeostatic perturbations at the subsequent higher levels (see **Fig. 2).**

ADAPTIVE RESPONSES

In general, single perturbations of homeostasis at a given level physiologically trigger, if damage is involved, immediate repair reactions in order to reconstitute structure and function quickly. Mild to moderate perturbations also initiate reactions that with a delay of hours temporarily for days to months equip the system with a certain degree of protection against continuing exposure to a toxic impact including that arising from lower levels. The consequence is temporarily a higher level of resistance against toxic impacts. Type and degree of this adaptive protection depends on the organizational level, where the perturbation occurs. **Figure 3** lists known adaptive protections at the various levels of biological organization after acute exposure to toxic impacts at various levels. Adaptive protection is quite common in toxicology and provides for a benefit also termed hormesis; this is now generally well recognized **[13].**

Common examples of consequences of adaptive protection are personal individual experiences with exposure to UV light, with protective tanning, and eventually serious sunburns and blisters with increasing exposures to the sun. Another common example is immunization by low quantities of pathogenic microbes and illness with large quantities. Or certain chemicals at low doses may be "medicines", whereas they are poisons at high doses, such as vitamin D. An example of protective response to repetitive mild to moderate perturbations is what is generally understood by the term training. An athlete gains in performance by repetitive demands on his body in such a way that regular exercise at certain intervals imposes homeostatic perturbations that lead, for instance, to body building.

Adaptive protection following low-dose irradiation includes in ascending order from lower to higher levels of organization **[14, 15]**: up-regulation of scavenging mechanisms in order to prevent a toxin such as reactive oxygen species, ROS, from reaching its targets such as DNA; enhanced and/or improved repair of damage such as of DNA damage; and induced removal of damaged cells. The latter includes immune responses and signal induced cell death, apoptosis, the mechanism of which may involve low-dose induced reduction of signal inhibition **[16].** Damaged cells may also exit the system by terminal differentiation to function with a short life expectancy. Each response, of course, involves or again creates inter- and intracellular signaling. In principal, each type of adaptive protection except for apoptosis appears to reach a maximum at a defined level of homeostatic perturbation and all have a particular duration **[14, 15, 17].** The various forms of adaptive protection except apoptosis disappear when perturbations become increasingly destructive.

It follows that damage as it continues to rise with the instantaneous number of impact increments at the basic level of organization, increasingly prevails over protection after the protection maximum. It is noteworthy that regarding x- or γ-irradiation adaptive protection except apoptosis increasingly fails above a single dose of about 0.1- 0.2 Gy in mammals **[14, 15, 17]** . There is a rather narrow range of radiation doses where protection maximum of the various protective responses occurs after exposure. A reason for this may be the involvement of cells in moderating signals from any level of organization **(see Fig. 2).**

If mild to moderate toxic impacts occur repeatedly, the responses of homeostatic systems vary depending on the time interval at which the systems are perturbed. Varying the time interval between two consecutive toxic impacts may either enhance or limit the full expression of adaptive protection of any type in the system. The time intervals may be long enough for a perturbation not to interfere with an adaptive protection to a preceding perturbation **[18]**. On the other hand, the time interval between two consecutive toxic impacts, such as energy deposition events to a target in a chronically irradiated system, may become unfavorably short so that the second impact interferes with the response to the first. In this case, damage may outweigh any protective effects from individual impacts, and simple or super-additive damage accumulation may occur **[3]**.

Following low-dose irradiation, adaptive protection in response to non-destructive perturbations of homeostasis

in a biological system also functions against toxins that are from a different source but impact similar targets, for instance, against the reactive oxygen species (ROS), which arise abundantly and constantly in every cell by normal oxygen metabolism **[19, 20].** If the consequences of radiogenic protection against endogenous toxins outweigh radiogenic damage, then a net benefit results, a hormetic effect.

ADAPTIVE PROTECTION AND RISK

Adaptive protection at all levels of biological organization reduces temporarily not only the risk of a certain damage to recur upon repeated exposure to an impact increment, but also the effectiveness of propagation of damage to higher levels of organization. As stated above, the probability of damage propagation from lower to higher levels is not constant per increment of effect or damage at a lower level. The reason for this lack of constancy, again, is the property of homeostatic systems to respond maximally to certain degrees of perturbation and then become ineffective as damage prevails over protection. With perturbations ascending from lower to higher levels, corresponding adaptive protection of various kinds appear and an example is the induction of immune responses **(see Fig. 3)**. Induction of immune responses fails as absorbed doses increase beyond about 0.1 - 0.2 Gy. Individual adaptive protection, indeed, depends on the degree of perturbation, and the higher the degree of perturbation the more likely becomes system failure.

From what has been stated it is clear that there is lack of proportionality between incidence of damage at higher levels of organization such as cancer incidence and the multitude of impact increments such as energy deposition events from ionizing radiation at the lowest level. It may be assumed that malignant tumors arise from stem cells and hat induction of primary damage to DNA in stem cells is principally similar to that in any dividing cell. Moreover, there is proportionality between the numbers of DNA damage and the numbers of average energy deposition events of a given size in culture under defined investigational conditions **[3].** Under these justified assumptions the relationship between the numbers of primary DNA damage in stem cells to the incidence of clinical cancer is not linear. Indeed, the probability of clinical detriment is the consequence of both the multitude of damaging responses and the degree of various forms of protective responses per number of primary toxic impact increments at the basic level of organization such as the DNA **[14, 21].** Concretely, the risk of detriment at the highest level such as cancer depends on the relationship between the probabilities of cancer-causing to cancer preventing responses elicited by the various numbers of energy deposition events from ionizing radiation in the exposed system. A corresponding mathematical model expresses this relationship **[14, 15].**

Even under the premise of a constant relationship between numbers of impact increments at the lowest organizational level and of derived clinical effects measured at any value of absorbed dose, the power of a complex system to resist damage propagation to higher levels is quite obvious from data given in **Figure 4**. This figure displays in summary well studied effects in the blood-forming system at the various levels of biological organization for the case of low-dose exposure to x- or γ-irradiation **[5, 14, 15].** The data in **Figure 4** derive from the following inputs: - an absorbed dose of 1 mGy 100 kV x rays to the bone marrow of man, which contains a total of about 1.5×10^9 stem cells; - experimentally measured effects in the exposed tissue as a function of linear relationship between doses and effects; - extrapolation of all data individually measured at high doses to be valid at low doses per single stem cell average. With these inputs, the quotient between the probabilities of DSB and radiation-induced lethal leukemia per impact increment of 1 mGy to bone marrow stem cell average is about 10^{12}. If damage amplification would occur even by a factor of 10, for instance at the cellular level in terms of bystander effects and genomic instability, the above given probability of a DSB to cause lethal leukemia would change from 10^{-12} to 10^{-11} - a relatively insignificant change .

It is obvious from the high quotient of DSB over lethal leukemia per average bone marrow stem cell that the barriers to damage propagation from basic to higher levels of organization prevent not only damage amplification but also lead to damage disappearance.

Under the assumption of cancer to arise eventually from a single cell and knowing that the human genome per cell contains about 3×10^9 base-pairs and perhaps some 35 000 genes, each base pair in the DNA of a blood-forming stem cell must suffer a serious damage on average some 300 tines, or each gene some 30 million times, for one lethal leukemia to develop. The enormity of such numbers and the arguments above makes it senseless to state, as is often done, that each DSB is a potential cause of a malignant tumor.

Numerous experimental and epidemiological data show that low doses of toxins, including ionizing radiation, may cause not only less detriment than expected upon the linear-no-threshold hypothesis, but even initiate a reduction of spontaneously occurring clinical detriment such as cancer, a hormetic response, for instance, by low-dose induced adaptive protection against endogenous toxins **[19, 20]**. Indeed, "a number of recently published studies indicate that the hormetic dose response, when properly studied, is more common than other dose response models such as a threshold model" **[22, 23].**

CONCLUSION

For risk assessment in complex adaptive systems exposed to low doses of toxic agents, including radiation, both the damaging and protecting responses need attention. It is the multiple of the responses that determines the outcome. In returning to the example of the chisel on wood, the chisel on the wood of a living tree may cause damage, but the living tree tends to repair the damage and depending on the extent of the damage may alter leave sprouting and growth and thus raise crop. To exclude either protecting or damaging responses in favor of the other in risk assessment is scientifically unjustified and misleading. The quotation from a document by the Environmental Protection Agency (EPA) stating [**24]:** "..as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned" appears to be strongly biased, unacceptable to science, and a disservice to society.

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FIGURES

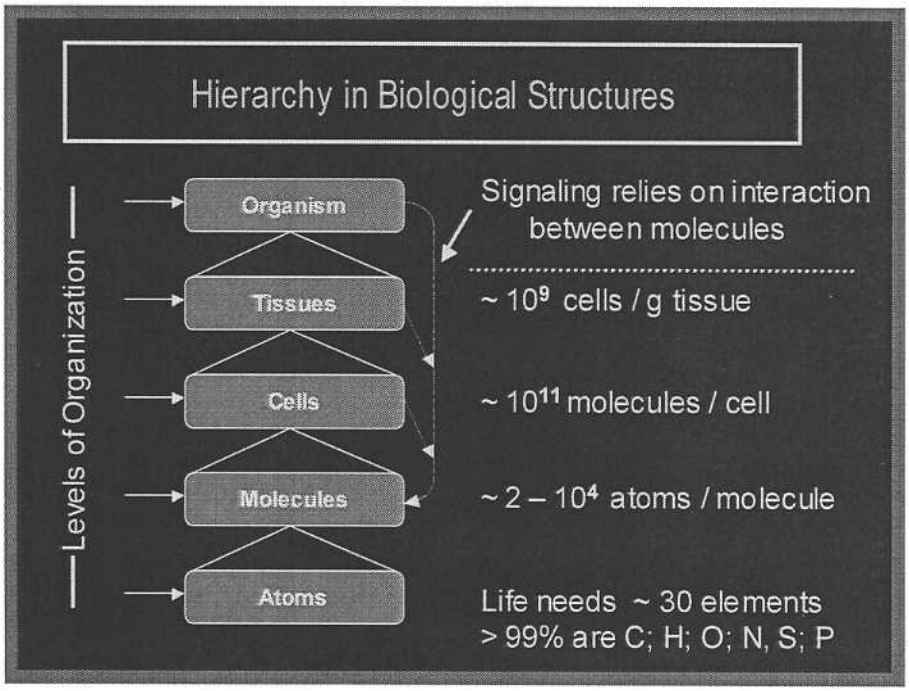

Figure 1.

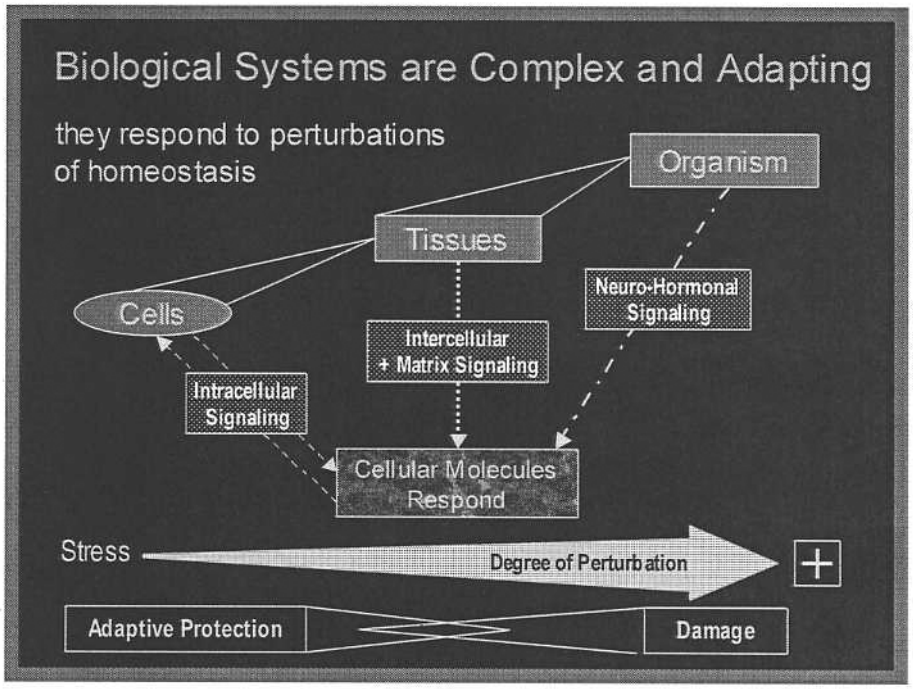

Figure 2.

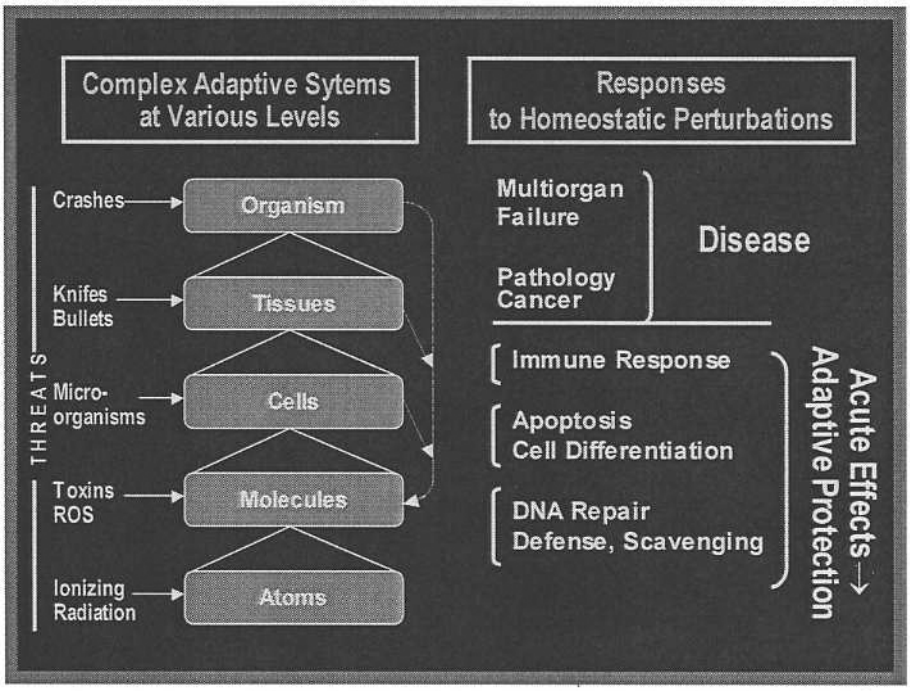

Figure 3.

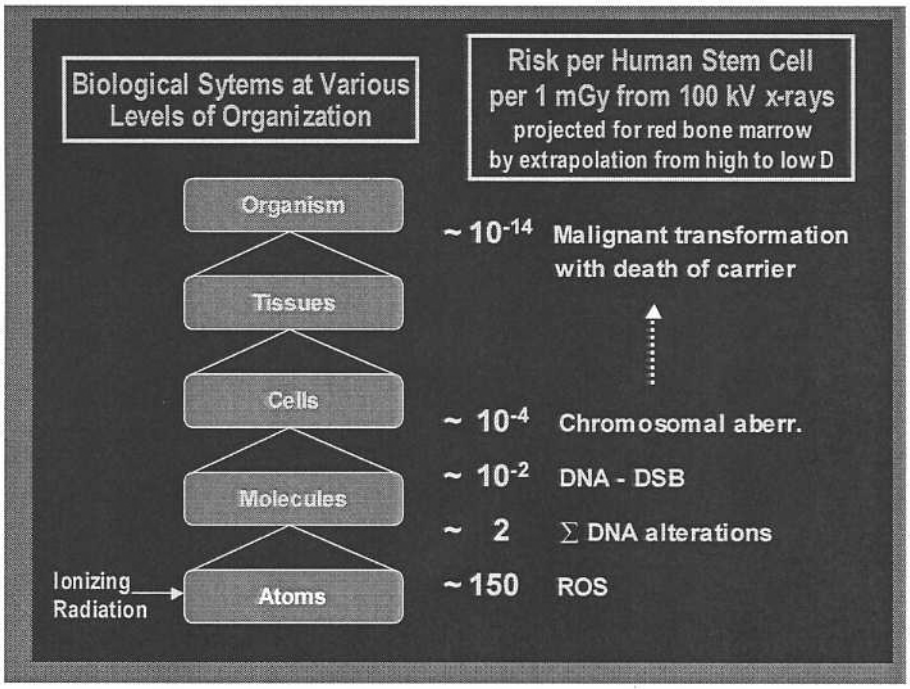

Figure 4.

A BRIEF COMMENTARY ON SECTION 4.1.3 OF THE EPA MARCH 2004 STAFF PAPER: AN EXAMINATION OF EPA RISK ASSESSMENT PRINCIPLES AND PRACTICES

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The U.S. Environmental Protection Agency (EPA) is to be commended for its recent initiative to pull together from various perspectives and articulate its current risk assessment practices[1]. This appears to be a reasonable step in the direction of understanding where ambiguity in risk assessment approaches may be clarified, methodological or conceptual weaknesses highlighted and addressed, and central principles reiterated. Section 4.1.3, entitled "Does Any Change Seen in Animals Indicate There Will Be a Problem for Humans?" presents a glimpse of EPA current treatment of the full range of responses to toxic exposures, including those considered adaptive or even beneficial. Examination of this section may determine whether the EPA's current risk assessment practices with respect to hormetic, or biphasic, dose-response risk functions, needs to be clarified, or if incorrect, fixed.

One argument in favor of clarification may be that the language of section 4.1.3 of the EPA Staff Paper is vague, and subject to multiple interpretations. Specifically the statement, "Moreover, as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned," might be viewed as a command prohibiting consideration of any response that does not constitute an increase in risk. On the other hand, it may not at all be an admonishment, but rather a reflection of current EPA risk assessment practice: in the process of describing the toxic effects of a substance, it is possible that the adaptive or beneficial effects are ignored or at least go unmentioned. That this sentence begins with "Moreover…" and follows the previous sentence affirming that "various experts may have differing opinions on what constitutes an adverse effect for some changes" suggest that this is a descriptive and not a prescriptive statement. Further, the language preceding this statement acknowledges that beneficial or adaptive effects indeed might exist, and that the focus of risk assessment has been on adverse effects (and this is reiterated throughout the Staff Paper). This supports a view that this section is not attempting to define or redefine the purpose of risk assessment, which is clear from the document overall, but rather to point out that the determination of adversity can be tricky, and "In cases where data are not available to determine when the capacities of repair mechanisms are exceeded and adaptive responses become toxic, health assessments are based on any adverse response that is deemed biologically significant" (third paragraph). This statement directly implies that where such data are available, the assessment could incorporate them and presumably improve the derived risk estimates.

The third paragraph is clearer, however, and concludes with the statement, "As a general principle, our practice is not to base risk assessment on adaptive, non-adverse, or beneficial events." This statement seems to be accurate, while not necessarily precluding the potential for a different approach or model – if and only if (consistent with other departures from default assumptions) convincing data exist. Interestingly, A Dictionary of Epidemiology[2] – viewed as an authoritative epidemiological reference – is narrower as it defines risk assessment as "The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences."

The larger question (apart from the actual intention of the language in section 4.1.3) may be whether the Agency should allow for adaptive or beneficial effects in risk assessments. Clearly, the public health community's awareness and acceptance of hormesis is growing, and more and more toxicologists and epidemiologists are finding a biphasic response model at least as reasonable as a linear or threshold dose-response model[3]. Whether this should impact EPA's risk assessment approach, however, is not clear at this time. From an epidemiological perspective, the relationship between epidemiological research and the risk assessment process is often strained, as the risk assessment process, with its heavy

dependence on mathematical modeling, easily can overlook even basic flaws in the design and execution of epidemiological studies, leading to acceptably precise (in a statistical sense) results that lend themselves to modeling but in reality are absolutely wrong. From this vantage, the inclusion of some provision for a biphasic response in the EPA risk assessment process (which is precluded in the presence of reasonable data) seems to be an objective similar to gaining acceptance for a threshold response for carcinogens – to be considered only if it can be scientifically substantiated.

Assuming that an erroneous default assumption of linearity were invoked, what impact would there be on the resulting risk assessment? First, and at least from epidemiological studies, there likely will be few reliable and valid risk estimates in the lowest exposure levels, so the question may be moot for most chemicals. As previously discussed, epidemiological studies typically ignore hormesis, often not intentionally, but due to methodological limitations[4]. If hormesis is present, the result is an exaggeration of risk, due to what we called the "hormetic bias." Briefly, hormetic bias results from classifying all individuals with exposure below a certain level as "unexposed" (or controls). Controls with nonzero exposures in the stimulatory range carry a lower risk than the truly nonexposed, resulting in an overall underestimate of the risk among the "unexposed" comparison group, and a subsequent overestimate of risks among all higher exposure groups. These biased study results, incorporated into a standard risk assessment, will translate into artificially elevated unit risk estimates, another conservative – and therefore politically acceptable – bias.

In the context in which epidemiological data are of adequate quality to validly exhibit a hormetic response, ignoring the reduced risks associated with the hormetic range of exposure also would result in a conservative risk assessment[5]. However, in this setting, the specific risks associated with higher exposure levels would not be overestimated, but those at the low end would be. Of course the greatest accuracy in risk assessment might be desired, but there are numerous important sources of uncertainty in the use of epidemiological data in risk assessment. If an adequate body of valid epidemiological data on a specific chemical were available, and supportive of a hormetic response, then it would be critical to reexamine risk assessment methodologies to properly factor in the biphasic response, as enormous public health resources are certainly devoured – often rightly so – in the interest of conservatism.

The Staff Paper acknowledges many of the other concerns epidemiologists often raise regarding risk assessment, including the historic levels of conservatism, risk assessment for multiple exposures, susceptible subpopulations vs. average risks, etc. Within these discussions are additional opportunities to consider whether the acceptance of biphasic dose-responses necessarily leads to the need for an alternative, nonlinear base model, especially where data are lacking. Are there good examples from animal studies demonstrating a hormetic response that risk assessment would be different from that in which a linear low-dose extrapolation is used? Would this be materially different from a model assuming a threshold (i.e., no adverse effect below a specified dose)?

EPA is likely to maintain the current default models, unless there are reasonable scientific data to do otherwise. Clearly these defaults might be incorrect, in which case the results tend to be conservative – a position understood from the outset of the risk assessment process. Similarly, the presence of an underlying hormetic response when the default assumptions are invoked will lead to an additional measure of conservatism, more so in cases where LNT models (i.e., for carcinogens) are assumed and to a lesser extent under a threshold model (i.e., for non-carcinogens). In these cases the risk assessment practices appear not to be broken, but certainly in need of clarification and eventually further development and refinement. On the other hand, the lack of real understanding of exposure-response relationships at extremely low levels of exposure represents an area of ambiguity that first must be clarified with substantial additional high-quality research directed at the low-end of the exposure continuum.

EXAMINING THE RISKS AND BENEFITS OF CONSIDERING BOTH THE TRADITIONAL DOSE-RESPONSE AND HORMESIS IN ARRIVING AT AN ACCEPTABLE EXPOSURE LEVEL

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In a recent review Calabrese and Baldwin [1] state that hormesis may be adopted as a default response it offers improved explanations or means to solve problems [1-3]. We submit that if in addition to adding information, it allows animals or persons exposed to experience the beneficial effects of hormetic exposure, it will be more likely adapted as a default response to replace the traditional dose-response. However, the issues as to what constitutes a beneficial response, or is an adaptive one which may provide both benefits and risks, or is a response clearly on the path to maladaption, for which there is no discernible benefit are not at all clear.

The basic question that governs what constitutes the risk assessment process and the types of data used was discussed in a recent document entitled "AN EXAMINATION OF EPA RISK ASSESSMENT PRINCIPLES AND PRACTICES", a Staff Paper prepared for the US EPA by Members of the Risk Assessment Task Force (EPA/100/B/001) March, 2004 — Section 4.1.3 (page 53). The purpose of a risk assessment was given as defined in the paragraphs below [2].

In responding to the question, "Does any change seen in animals indicate there will be a problem for humans?": From one perspective, "It is generally accepted that there can be numerous changes to the recipient organism (the animal under study) following exposure to a chemical, some of which may be beneficial, adaptive, early manifestations on a continuum to toxicity, overtly toxic, or several of these things in combination. Unless there are data to indicate otherwise, a change that is considered adverse (i.e., associated with toxicity) is assumed to indicate a problem for humans". From a second perspective, "It is recognized that a diversity of opinion exists regarding what is '*adverse*' versus 'adaptive,' both within EPA and in the general scientific community. At present, there is no Agency-wide guidance from which all health assessors can draw when making a judgment about adversity. Therefore, various experts may have differing opinions on what constitutes an adverse effect for some changes. Moreover, as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned".[2]

It is important that beneficial hormetic effects be mentioned in the risk assessment process. Calabrese and Baldwin have devoted considerable effort to clarifying the nature of the dose response in the low dose zone [1, 3-6]. The hormetic dose response is common in the toxicological literature when studies are designed to assess below NOAEL responses. Studies using below traditional NOAEL doses demonstrate reduced background disease incidence, yielding what many would call a beneficial effect. In fact, a number of recently published studies indicate that the hormetic dose response, when properly studied, is more common than other responses [1, 3-6]. For this reason scientists outside EPA were asked to comment on the statement of the EPA staff paper – to explore, discuss and evaluate it.

Calabrese and Baldwin believe that hormesis provides more and improved information for problem solving [1, 3-6]. Others agreed [7-10]. If one examines Hewitt's figure 1, forcing concentrations to be $\leq$ the NOAEL would cause the organism to lose some of the beneficial response that would accrue if the beneficial hormetic response were taken into account. [8-10]. Data in the figure argues against the assertion by EPA that any change is an adverse effect, and therefore a problem for humans.

Hormesis' description of low level beneficial effects adds a positive aspect to the dose-response which will help in solving problems. For example, it has helped identify nutritional essentiality [11-14], and has the possibility of identifying still more. Secondly, it helps us understand the connections of stress and readiness to the zealousness of general defense reactions [11-14].

Qualitative dose response indicates that an increasing dose to target tissue leads to increasing toxicity [8]. To this assertion, hormesis adds that at concentrations ~20% of the NOAEL, toxins produce beneficial homeostatic responses. This beneficial response is related to an enhanced host immune (defense) effect and an enhanced ability of the host to repair damaged cells [2-6]. In this uncomplicated form, this information is exciting. It will not only add useful information for problem solving, but also provide concentrations experiencing a beneficial response

The issue is not whether the beneficial change will at higher doses become non-functional, but whether it is truly beneficial to the animal or person at this level, a level which is in the low dose range near the level of the NOAEL. Alternatively, this change may not provide a clear advantage for the animal or person. To more fully understand the benefits and implications of hormesis, toxicologists or risk estimators must take into account both the benefits, reduced risks, the upsides as well as the the added risks, the downsides of low-level toxicologic stimulation, and the increased healing capability.

DISCUSSION

To decide the degree of complexity of the hormetic response, we offer several case scenarios.

Case 1. Inhaled Carbon Black.

This dose-response is a product of the dose of carbon black to the pulmonary parenchyma, and the response of the species in which it is delivered [15-16]. Hamsters exposed to carbon black developed a mild transient hyperplasia of pulmonary alveolar type II cells after 1 day of exposure. This change was absent after 13 weeks of the same exposure. Fischer 344 rats responded more vigorously than F1B hamsters and developed lung tumors from chronic exposure to the same levels of carbon black aerosols. Hamsters have a vigorous pulmonary defensive response. Type II alveolar pneumocytes were stimulated by the carbon black exposure [18, 19].

Here we ask the question, "*Is the transient hyperplasia of hamsters in response to carbon black a beneficial response, an adaptive one, or a response which is on the way to poor adaptation"*? In the case of Fischer 344 rats, the development of tumors was a harmful response or unacceptable adaptation. This response seems adaptative which is reversible for F1B mice. Alternatively, one might make the argument that there is an as yet unknown benefit in the increase in type II alveolar cells which disappears when the challenge of inhaling carbon black no longer requires it. These responses were more an adaptation than the many responses reviewed by Calabrese and Baldwin [1, 3-6]. After considering both the potential of benefit of hormesis and the conventional dose response, one can see this response could have been described by the conventional dose response.

Case 2. 3-Methyleneindolenine (3MEIN)

The toxic metabolite of 3-methyl indole, 3MEIN, stimulates pulmonary alveolar type II pneumocytes at lower concentrations, as indicated by type II alveolar pneumocyte hyperplasia in cattle affected at the lowest dose. Such cattle die when stressed, but most survive and recover uneventfully if monitored without stress [17-18]. At higher doses of 3MEIN cattle die of acute respiratory disease within 6-24 hours [17-18]. This pattern closely fits that of hormesis. It makes sense that type II alveolar pneumocytes making surfactant and repairing damage to the alveolar membrane by differentiating into type I alveolar pneumocytes would be stimulated by low concentrations of 3MEIN [17-18].

Here we ask the question, "*Is the permanent hyperplasia of hamsters in response to consumption of 3 MEIN a beneficial response, an adaptive one, or a response which could be considered no or poor adaptation"*? At higher doses adaptation did not occur (was prevented), so cattle commonly died in 6-24 hours. Alternatively, at lower doses, the response could occur but was not a reversible adaptation. The response at the lower dose was adaptation with very little benefit to the cattle. Thus, when we consider both the potential benefit of the hormetic response and the conventional dose response, the conventional dose response is the most appropriate in this case.

Case 3. Pulmonary Fibrosis

In considering the pathogenesis of irreversible pulmonary fibrosis, initially one sees damage to pulmonary capillary endothelium and/or type I alveolar epithelium [13, 18-22]. The best action following such injury is healing by primary intent, by proliferation of type II alveolar pneumocytes and by their differentiation into type I alveolar pneumocytes. Intact capillary vessels are needed. Connective tissue content of lungs are increased, but no fibrosis is present histologically [13, 18-22]. At higher doses and greater injury, pulmonary architecture is irreversibly changed and scarring develops [13, 18-22].
Increased proliferation to type II alveolar pneumocytes occurs at doses which do not lead to fibrosis. Hormesis describes an immune (defense) response which facilitates healing. The pathogenesis of early events is a zealous defense response which leads to healing, paralleling closely the hormesis paradigm. At still higher levels of injury, type II hyperplasia cannot form and animals die acutely of pulmonary edema. Increased numbers of type II cells provide increased preparation for higher doses and are adaptational. However, at low doses they provide little beneficial or detrimental responses and must be considered an adaptation.
Although the role of increased pulmonary collagen is not clear, one could make the argument that it provides structure to ground the increased numbers of pulmo-

nary type II cells or to act as a scaffold to support regenerating epithelium or endothelium. Lung collagen's increased presence adds information to understanding the pathogenesis of pulmonary fibrosis. It probably reflects a greater capacity for healing by secondary intent (fibrosis) and, thus, must be considered an adaptation as well. Alternatively, it is possible that reversible pre-fibrotic changes may add an as-yet-to-be-determined risk.

Case 4. Continuous Low Level Exercise

Let us consider the price of being always alert, focused, turned on, forever vigilant. Most of us might react by saying that we're not forever focused, yet the hormesis description of the dose response says that to a degree we may be [2]. Certainly, we must sleep, but our biological responses need not. Let's consider the possible effects of continuous low level toxicologic stimulation of hormesis. Initially, we expect a focused but heightened attempt or sense of sensory and physical discrimination [23-24]. Steady state exercise in healthy humans could mimic continuous central sympathetic stimulation [11]. Steady state exercise in humans leads to increased circulating noradrenaline and reduced variability of heart rate [23-24]. Continued stimulus causes partial desensitization of nicotinic receptors that leads to habituation and promotes dysfunction by continual occupation of desensitized receptors [16]. After sufficiently long stimulation, the possible degeneration or death of receptors must be considered.

The question before us is: "*Is the miniscule, protracted elevation of nor-adrenaline beneficial at this low level*"? Other than a general state of readiness and heightened sensitivity, there is little advantage in this elevation. There is a downside of desensitization of nicotinic receptors, and their eventual habituation and dysfunction. This result suggests that the change is adverse and provides advantage for using the NOAEL. This response is more of an adaptation than the many beneficial responses reviewed by Calabrese and Baldwin [1-5]

Case 5. Lead

Lead's affect on erythrocytes (stimulation of erythrocyte production, preceeding toxic inhibition at higher concentrations) might be beneficial or adaptative [25]. Lead is toxic to sulfhydryl functional groups of mitochondrial enzymes. It makes sense that lead would stimulate erythrocyte production as defense against vital enzyme inhibition at higher lead concentrations [25]. It also makes sense that if even low concentrations of lead were toxic to vital neurons, additional erythrocytes would carry more oxygen to such stressed cells. Alternatively, if this level of lead were too low to affect mitochondrial enzymes, it might be beneficial.

When we examine the neurotoxicity of lead using the functional intelligence quotient (IQ) in young children, a different picture emerges. There is no "safe" blood lead concentration; specifically, there is no concentration of blood lead below which IQ is not lost [26-27] (no threshold effect). Lead delays slightly the onset of mensuration in pre-menarchal human females. Again, no concentration of blood lead is sufficiently low to eliminate this effect. The reason(s) for this lack of threshold is unclear. However, when considering this response to low lead, there is no evidence that low lead levels are beneficial. Considering the hormetic and conventional dose response, although the hormetic response provides more information, it offers no benefit. Thus, the conventional model may be appropriately used.

Case 6. Diarrhea or Colorectal Cancer

In instances of colorectal cancer, ETEC shigatoxin-a binds to a receptor with guanylin or uroguanylin to alter a c-GMP gated channel that transforms proliferation of colonic epithelium into colorectal cancer. This is molecular mimicry, exploiting the normal physiology of colonic epithelium to promote the healing response [28-29]. As ETEC shiga toxicosis progresses, diarrhea may develop. This qualitatively fits the criteria of hormesis, providing information about low level collaborative responses to understand colorectal cancer pathogenesis and the microecology of ETEC; it demonstrates beneficial hormesis. To fully describe the response and accurately estimate risk relative to benefit, the hormetic response must be taken into account.

SUMMARY OF CASE EXAMPLES

We have described 6 situations. The first 3 cases were pulmonary: hyperplasia of type II alveolar pneumocytes was reversible following inhalation of carbon black in F1B mice but was permanent after 3 MEIN exposures and induced at low injury in the development of irreversible pulmonary fibrosis. In pulmonary fibrosis, hyperplasia of type II cells is accompanied by increased connective tissue collagen. Each of these cases represents adaptation. In pulmonary fibrosis, the adaptation provides capacity to heal, a potential benefit, but healing is by fibrous connective tissue – less desirable than healing by primary epithelial growth. Alternatively, one might make the argument that at a sufficiently low level, perhaps the NOAEL, capacity to heal is not needed. We call this adaptation as having no proven benefit beyond an added healing capacity. The reversibility of the adaptation after mice inhaling carbon black demonstrates this to be so. Thus conventional dose response can be used to estimate the allowable level of exposure.

Both the effect of continuous exercise on the sympathetic nervous system and the effect of low level lead exposures on erythrocyte function and central integrative neurons is adaptation, with no clearly demonstrated balance toward beneficial hormesis. Thus, in cases 4 and

5, conventional dose response can be used to estimate the allowable level of exposure.

In colorectal cancer, the ETEC shigatoxin reduces proliferation of colonic epithelium, showing molecular mimicry, and exploiting the physiology of the colonic epithelium to promote healing [28-29]. This qualitatively fits hormesis and provides information about low level collaborating responses providing an understanding of colorectal cancer and the microecology of ETEC. In this case, the healing response coincides with dose, and the benefit is obvious. Thus, added benefit accrues if hormetic changes are taken into account when estimating allowable levels for this compound.

CONCLUSIONS

All the cases we discussed are potentially hormetic. All provide increased information about the reactions if the hormetic features are considered. However, in only the ETEC shigatoxin case is there clear irrefutable evidence that beneficial hormetic properties exist and must be considered. We believe that one-in-six advantage is too great to ignore the potential benefits of hormesis; we recommend such hormetic properties be considered in estimating chemical risk. We believe that by considering both hormesis and conventional dose responses improved estimates of allowable exposure occur.

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FIRST DO NO HARM: CAN REGULATORY SCIENCE-POLICY IN RISK ASSESSMENT BE DELETERIOUS TO HEALTH?

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ABSTRACT

We contribute a constructive review of the US EPA science-policy on uncertainty and variability in human health risk assessment in the context of uses of evidence of adverse effects from exposure to noxious agents. We propose that the US EPA can decrease its reliance on default values and assumptions, particularly when these relate to uncertain causation, by more fully using decision-theoretic methods and criteria that explicitly account for scientific beliefs and can be fully studied by either advocates or adversaries of a policy choice, in *administrative* decision-making involving risk assessment. The substitution can account for the risk aversion, neutrality or even proneness of the stakeholders in any policy debate, with the added advantage that those become clear and explicit and can thus be understood by the public and risk managers. Moreover, this change provides a sound scientific way explicitly to account for new knowledge and the effect that this new knowledge will have on eventual policy choices. Although these improvements can complicate regulatory analyses, the danger of not moving beyond defaults is that costs to society of default-motivated actions may be disproportionate to their benefits, while beneficial effects from exposures to low doses (e.g., from hormesis) may not be adequately weighted in informing policy choice. To avoid these drawbacks, an agency's choice of numbers to be used in risk assessment should rest on sound theoretical and empirical analyses and criteria, rather than on the heuristics typically used in consensus-based and default-driven choices. There is legal precedent in environmental and administrative law for shifting from a consensus-based approach to more data-driven methods grounded in decision analysis. The increase in administrative burden that these methods might impose on the agency is likely to be more than offset by the improvement in the efficiency and effectiveness of regulations in achieving desired goals.

INTRODUCTION

A primary goal of public health risk analysis is to identify what risk management interventions are expected to protect and promote human health, given currently available information with all its imperfections. Within risk analysis, health risk assessment quantifies the probable human health consequences of alternative risk management interventions – consequences that usually can be expressed in terms of changes in the rates of mortalities, morbidities, illness-days of varying degrees of severity, or summary measures such as quality-adjusted life-years (QALYs) lost per year in the population. This paper argues that, in many situations, preventing low-level exposures to hazards, a seemingly intuitive and reasonable strategy for protecting human health, can cause unintended harm to human health if alternative causal theories (such as hormetic dose-response relations) not adopted as defaults by an agency are correct. In such cases, prudent risk management (and sound decision analysis) may require *hedging one's bets* against scientific uncertainty. This requires acknowledging more than one possibility and taking actions that are *optimal* (e.g., that maximize expected utility, or at least that are stochastically undominated by other available actions) with respect to a *set of alternative possibilities*, rather than with respect to a *single set of default assumptions*. More specifically, any regulatory approach that relies on default assumptions when alternative, conflicting causal hypotheses are plausible, violates widely accepted, theoretically sound principles of risk assessment and risk management, produces less-than-optimal decreases in

human health risks, and in this way fails to serve the public interest.

For example, one view is that holistic perceptions and beliefs about the relative "badness" or seriousness of different types of hazards should drive regulatory or quasi-regulatory approaches, such as guidelines. By contrast, in our view, rational choice among alternative risk management options requires comparing *probable consequences* of the different decision alternatives, e.g., the changes they cause in frequencies and severities of resulting adverse health outcomes. Consensus perceptions about how important different environmental agents are in human health, or about which hazards are best and worst (or are most and least risky or severe) in some holistic sense, are simply not appropriate grounds for guiding rational (consequence-driven) action. Accordingly, regulatory guidance and proposals to base risk management decision recommendations on judgments or perceptions about a current situation – which may be labile and subject to manipulation by media-savvy interest groups – rather than on estimates of how alternative decisions would change current health risks, provide inadequate frameworks for guiding sound regulatory policy. In short, assessment of probable consequences of actions, not the importance of the concerns that motivate them, should be the guide for choice among risk management actions.

THE US EPA, SCIENTIFIC EVIDENCE, AND RISK ASSESSMENT

We focus on the US EPA's policy-making process (US EPA, 2004) and on its most recent science-policy basis for ameliorating human environmental health through risk assessment. We address several science-policy issues, rather than the justifications for "potency" factors, RfDs and other measures used to achieve the US EPA's risk goals. Our analysis begins with the statement that (US EPA, 2004, Section 4.1.3, p. 53):

> "It is generally accepted that there can be numerous changes to the recipient organism (the animal under study) following exposure to a chemical, some of which may be beneficial, adaptive, early manifestations on a continuum to toxicity, overtly toxic, or several of these things in combination. Unless there are data to indicate otherwise, a change that is considered adverse (i.e., associated with toxicity) is assumed to indicate a problem for humans. … At present, there is no Agency-wide guidance from which all health assessors can draw when making a judgment about adversity. Therefore, various experts may have differing opinions on what constitutes an adverse effect for some changes. **Moreover, as the purpose of a risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned." (Emphasis added)**

We disagree that "the purpose of a risk assessment is to identify risk". That is an important goal of *hazard identification*, which seeks to identify adverse effects caused by exposures. But this is only one component of risk assessment. The main practical purpose of risk assessment as a whole is to *provide information needed to improve risk management decision-making*, i.e., needed to help decision-makers choose interventions that are likely to result in preferred consequences. It does so by assessing the probable human health consequences of alternative risk management interventions. From this perspective, it is essential to address the risks *caused* by interventions as well the risks *prevented* by them, in order to give decision-makers a full and balanced accounting of the likely health impacts of their actions. We study some of the implications of these statements by reviewing how variability and uncertainty associated with data and theory can be assessed (analyzed and evaluated) in sound decision-making under risk or uncertainty. In particular, we focus on the emphasized part of the previous statement as well as on the US EPA assertion that it (US EPA, 2004, p. 3):

> "conducts risk assessment to provide the best possible scientific characterization of risks based on a rigorous analysis of available information and knowledge — that is, a description of the nature and magnitude of the risk, … a summary of the confidence or reliability of the information available to describe the risk, … Risk assessment, therefore, informs decision makers about the science implications of the risk in question. Risk assessments that meet their objectives can help guide risk managers to decisions that mitigate environmental risks at the lowest possible cost and which will stand up if challenged in the courts." (Emphasis added)

We see some conflict between these assertions. Moreover, we suggest that risk assessment should inform decision makers about the health consequence implications of the risk management interventions being considered, not just "about the science implications of the risk in question." We also believe that "the best possible scientific characterization of risks" (like the ontological argument for the existence of God) is not necessarily a well-defined or uniquely defined concept, nor the most useful one for applied work. Rather, the humbler goals of *conditioning* probabilistic risk assessments on available information, however imperfect, and *identifying undominated decisions*, given current information, should be the chief concerns of regulatory risk assessment. We find that these considerations have the necessary grounding in environmental and regulatory law of the United States, a sine-qua-non concern in science-policy[1] in risk assessment. Unlike scientific arguments based on universal laws, our discussions focuses on American regulatory law (i.e., administrative and environmental), which differs from the law of other national jurisdictions, because the importance of US EPA-based regulations extends well beyond the United States. Legal aspects of risk assessment result from legal (legislative) actions, interpreted by the US EPA and issued as either standards or guidelines, and can be reviewed by the courts when a

controversy arises, as would be the case where the agency choice of data or model is unacceptable to a regulated entity. Thus, studying US risk assessment is equivalent to studying science-policy, which is at the intersection between American law and the use of science, to justify a choice of guideline or regulatory risk number.

The "Best Possible Characterization of Science" at the Intersection of Science and Law.

It would appear that *the best possible scientific characterization* of risks should include conditioning risk estimates on recent advances in scientific knowledge, provided that this knowledge has been confirmed through successive, generalizable empirical and theoretical findings and publicly scrutinized via peer reviews or other critical examinations. Yet, because the US EPA must also meet the constraint that their science-policy work must withstand judicial scrutiny, it imposes a policy bias that conflicts with *the best characterization of risks*. In other words, if an agency has to prevail in court, it may be strategic not to use new evidence that can damage its case by being inconsistent with past court rulings. As we will show, it has not been demonstrated that the administrative coupling of "best science" to regulatory policy-making and judicial reviews necessarily yields optimal social outcomes. Moreover, an important function of a public agency is to inform the public and the stakeholders affected by its regulations or other, less formal, adjudications. Recently, the dissemination of biased scientific information by federal agencies became the express concern of the Congress and led to the Data Quality Act, DQA, (2002, not codified; P.L. No. 106-54, §515; Stat.2763A-153, 2000), amending the Paperwork Reduction Act (44 USC 3501 et seq.). Congress' concern was raised by the number of requests for data from the public and the fear that the information provided by the agencies that fall under this congressional mandate (executive departments and so on) could be incorrect and possibly cause damage to society. "Information" is defined in the DQA to include "statistical information". The DQA has been interpreted by the Office of Management and Budget (OMB) and formalized through its Guidelines (67 FR 8452). Specifically, "quality" is a composition of "integrity, objectivity, and utility" of the information (67 FR 8659). On the surface, the US EPA appears to meet the OMB guidelines, which state that information needs to be "objective, realistic, and scientifically balanced" (US OMB, 2002; 67 FR 8452). In addition to theoretical reasoning about cause and effect, under the DQA and the OMB's Guidelines, US federal agencies must use "sound statistical methods." There is no limit to the methods that may be used, other than they are sound[2]. "Sound" has explicit meaning in logic (as logically valid *and* producing true conclusions from true premises) and thus we suppose that this is what the OMB means by the term. Corroborating one of our central points, the OMB's Guidelines regarding "influential, scientific … statistical information" indicate that such information must be reproducible; it follows that hormetic or non-linear dose-response models that are sufficiently supported by theory and empirical data and are reproducible (in that the data withstand independent corroboration and the same effect is found across settings by different investigators) meet the OMB's criterion. Fortunately for our discussions, the scientific basis of alternatives to the default causal models used by the US EPA meet *Daubert* (Ricci and Gray, 1998) and other judicial opinions dealing with the *admissibility* of scientific evidence (Ricci and Gray, 1999) resolved by the US Supreme Court, for cases tried under federal (but not necessarily state) jurisdiction. The US EPA must conform to this legal framework. However, it remains to be proven that its policy-making results in "objectivity, realism and scientific balance". For example, it is well known that peer reviews can be biased, that group-think can affect peers as well as others, and that many peer-reviewed articles each year end up being corrected or retracted. In the context of public decision-making, it seems appropriate that the standards of review should be greater than the standard of scientific peer review of journal articles because the stakes for society are far higher than the mere acceptance or rejection of a paper in the literature. Central to causal reasoning for risk assessment, several empirical investigations (e.g., Ottenbacher, 1998) have shown that peer-reviewed articles in epidemiology commonly fall short of good statistical practices that would limit false positives to reported nominal rates, while many other commentators have noted that causal inferences drawn in peer-reviewed epidemiology and risk assessment papers often fall far short of the normative requirements for valid causal inferences (e.g., Weed and Gorelick, 1996).

Objectivity of scientific information is an essential component our discussion because it combines the *substance* and *presentation* of information and thus should be unbiased, accurate and so on. Thus, if an agency or any other official group (impacting societal well-being) involved in a regulatory risk assessment fails to account for new scientific information that can contradict its own default assumptions or conjectures, its conclusions are apt to be biased and the onset of group thinking may undermine its ability to discern and serve the public interest. As we will discuss, this is true regardless of the deference that a court may appropriately give to an agency's scientific judgment, when that judgment is based on impartial conditioning on relevant data, e.g., using techniques such as Bayesian model averaging (BMA), to account for uncertainties about which of several competing and conflicting models are correct.

An important principle of regulatory science-policy is that agency actions can be reviewed by the judiciary. When this occurs, generally if the stakes are sufficiently high, a great difficulty is that the courts have to contend with complicated uncertain causal arguments based on scientific evidence that can range from molecular

biology to epidemiology, as well as with a number of scientific judgments made by the agency under scrutiny. On a variety of grounds, courts have shown great deference to the scientific judgments made by an agency, often limiting their enquiries to determining if that agency has followed *procedures* in reaching its conclusions. This is in part why agencies can adopt policies that are not state-of-the-art. The judicial rationale for not reviewing in depth the science-base of a regulatory action, but focusing instead on procedures, was articulated by Judge Bazelon in *Ethyl Corp.* v. *EPA*, 541 F.2d 1 (DC Cir, 1976b) in a seminal statement for regulatory and administrative law:

> "Because substantive review of mathematical and scientific evidence by technically illiterate judges is dangerously unreliable, I continue to believe that we will do more to improve administrative decision-making by concentrating our efforts on strengthening administrative procedures."

Judicial arguments that require "strict proof" would fatally cripple an agency rulemaking and can be unhelpful when the real issue is how to take current actions that best hedge societal bets against scientific uncertainties, rather than establishing "strict proof" for any particular theory (DC Cir, 1986). The alternative to the "soft glance" is Judge Leventhal's "hard look," also in *Ethyl Corp.,* and reviewed by many commentators (e.g., Ricci and Gray, 1998; 1999).

Judicial Deference to an Agency Science-policy

It has long been established that "causation is key in environmental law," as was held in *Env. Defense Fund* v. *EPA*, (548F.2d 998 D.C. Cir, 1976a) and that, in the presence of a "great mass inconsistent evidence," the agency can find support for its ultimate decision to regulate, provided that that support has sufficient evidence (DC Cir, 1973). For instance, the US Nuclear Regulatory Commission was held free to adopt conservative assumptions by risking error on the side of overprotection rather than under-protection when those assumptions have scientific credibility (1982). The court accepted that the Commission's bounding of that risk to somewhere between one in two thousand and one in fifty million was appropriately left to the Commission's discretion. Reversal of an agency action requires an egregious error. For example, in *Motor Vehicle Manufacturers' Assoc. v. State Farm Automobile Insurance Co.,* 463 U.S. 29 (Supreme Court, 1983c), the Supreme Court held that an agency can be reversed if it:

> "relied on factors which Congress had not intended … entirely failed to consider an important aspect of the problem, offered explanations that run counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in point in view or the product of expertise."

Consider *Baltimore Gas and Electric, Co. v. Natural Resources Defense Council,* in which the Supreme Court unanimously reversed the DC Court of Appeals holding that the US Nuclear Regulatory Commission had acted arbitrarily and capriciously (Supreme Court, 1983a). The Court held that a "most deferential" approach should be given an agency engaged in making legitimate predictions of risks that "fell within its area of expertise at the frontiers of knowledge" and when the "resolution of fundamental policy questions lies with the agency to which Congress has delegated authority". However, there must be a "rational connection with Congressional intent". That is, an agency's rulemaking is limited by the objectives dictated by the legislation, by the substantial evidence test (discussed next) applied to the facts, and by the need to avoid being found arbitrary and capricious – a test that also applies to policy judgments and informal rulemaking. For instance, if an agency fails to comply with its own procedures, as in not submitting its findings to peer review, the court may even find this error to be harmless, as the DC Circuit concluded in the review of the setting of the ozone standard under the Clean Air Act (DC Cir, 1981). That court stated that safety factors are appropriate when certain groups of individuals are less resistant, and thus more susceptible to injury from ozone exposure, than the rest of the population and when there is no clear threshold. A more recent statement of the "arbitrary and capricious" test (found in the Administrative Procedures Act, 5 U.S.C. § 706(2)(A)) is that a court "will reverse an EPA action only if it is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law'" (DC Cir, 1992). With respect to judicial deference, the courts "will give an extreme degree of deference to the agency when it 'is evaluating scientific data within its technical expertise'" (DC Cir, 1996). Nonetheless, the courts must "ensure that the EPA has examined the relevant data and has articulated an adequate explanation for its action" (DC Cir, 1992).

Yet, scientific evidence in complex causal arguments based on conjectures can trip an agency's decision-making. For example, in *Gulf South Insulation, Inc.* v. *Consumer Product Safety Commission* (5th Cir, 1983b), the Consumer Product Safety Commission, in the rulemaking to reduce indoor exposure to formaldehyde, proposed to ban it because the evidence from an animal study involving approximately 250 rats suggested that the risk to humans of nasal cancers could be up to 51 carcinomas per million individuals exposed. The Commission had used the multistage model for cancer, and found that the approximate 95% upper confidence limit risk was too high; it was legally unreasonable. The court struck the ban down because it held that the record as a whole did not support the agency's finding under the *substantial evidence* standard. This standard, the court held, is more restrictive than the general standard of judicial review. A more complete statistical study (such as a randomized study) and a more thorough investigation of the biological basis associating formaldehyde exposures with cancer might have met the substantial evi-

dence test. The court found that eleven epidemiological studies were negative; this strongly influenced the striking of the ban. The "substantial evidence" standard was earlier used to rule against OSHA, in *Texas Ind. Ginners Assoc. Inc.,* v. *Marshall*, 630 F.2d 398 (5th Cir, 1980) where the claimant wanted to introduce into the docket, at the rule-making stage, a study which showed no adverse effects from industrial exposure, but OSHA refused to accept that inclusion. The court held that the study should have been included.

To understand what an environmental statute can require from the US EPA, consider the Safe Drinking Water Act (SDWA), which states that:[3]

> "… 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 (if the reliability of the method and the nature of the decision justifies use of the data)."

In litigation under the SDWA, the *Waukesha* court was deferential to the US EPA's decision to use the FGR-13 model because the agency's choice of dose-response model was well-reasoned and showed a "rational relationship to the characteristics of the data to which it is applied" (DC Cir, 2003). The justification for this interpretation (namely, the term rational) is *Nat'l Wildlife Fed'n* v. *EPA* (DC Cir, 2002b), where it was held that:

> "We may reject an agency's choice of a scientific model 'only when the model bears no rational relationship to the characteristics of the data to which it is applied." A very similar justification is found in Am. Forest & Paper Ass'n, Inc. v. EPA (DC Cir, 2002a), in which the ''rational relationship'' standard lead to the upholding of EPA's "reasoned preference for one methodology of calculating safe exposure levels over alternative methodologies were deemed sufficient."

In *Waukesha*, the D.C. Court of Appeals held that:

> "EPA adequately explained, based on scientific data, why it prefers the FGR-13 model and the epidemiological data it used over the dial painter studies and the approaches based thereon that petitioners endorse. Further, … the SAB, [US EPA Science Advisory Board] … reviewed and approved the FGR-13 methodology … ."

The *Waukesha* court then concluded that there was "substantial scientific support" on which EPA relied for selecting the FGR-13 model (and, in particular, its LNT, linear, non-threshold dose response model for radiogenic cancer). *Waukesha* is opposite to an earlier case, also under the SDWA, in which the D.C. Court of Appeals decided against the US EPA (*Chlorine Chemistry Council* v. *EPA*, 206 F.3d 1286 (DC Cir, 2000)). The court determined that EPA's use of the LNT as a *default* violated the SDWA command for "best scientific evidence." Specifically, the court opined that the US EPA:

> "openly overrode the 'best available' scientific evidence, which suggested that chloroform is a threshold carcinogen,"

a fact that had been admitted by the EPA at trial (in the "oral argument," 206 F.3d at 1290, 1291.)

Although the next point is procedural, we think that it provides some additional insights in understanding how a reviewing court will look at the scientific record. The quote is a footnote in *Waukesha*:

> "Petitioners also contend in their reply brief that EPA violated § 1412(b)(3)(B) by failing to specify "an upper bound, lower bound, and central risk estimate" or to identify "the range of alternative risk estimates produced by other methods that use the dial painter studies," … and ignored the congressional directive "to inform the public of 'alternative risk estimates that put the regulation in broader public health context,' " id. (quoting S. Rep. No. 104-169, at 29). Because this argument was raised in the opening brief only summarily, without explanation or reasoning, … it is waived."

Against this legal science-policy backdrop, it is increasingly clear that agency's actions should be more formal in their development of causal reasoning so that the public and the courts can be more confident in their understanding of the scientific basis of uncertain causation. This concern is now part of a federal statute that motivates the US EPA dissemination of scientific information.

Under the OMB's Guidelines, the information provided by an agency should be such that members of the public must be able to form their own opinions about the objectivity of the information itself (e.g., was it published in a peer review journal, was it changed as the state-of-the-art changed, and was that change reflected in the agency's own accounts?). In this context, the agency's information and dissemination should be transparent and full. It readily follows that, if many journal articles support a theory that can change the direction of reasoning about the effect of low levels of exposure on human health, then an agency should conclude that that theory has withstood peer reviews and should either be incorporated in its policy-making as an alternative, or explicitly be discussed and rejected for clear reasons, provided in the "full" set of information used by that agency in either rulemaking or other less formal proceedings.

The many statutes under which the US EPA operates not only concern the media water, soil, air but also resources recovery, insecticides and many other aspects of environmental protection. Each has its own language regarding scientific evidence of causation, and therefore can be more or less constraining on the agency. In general, courts examine the science–base as it existed at the time of the rulemaking, and as is introduced by the parties, without attempting technological forecasts (Ellman and Sunstein, 2004).

Over and Under Estimation as Science Policy

The US EPA (2004, pp 12-13):

> "seeks to adequately protect public and environmental health by ensuring that risk is not likely to be underestimated. However, because there are many views on what "adequate" protection is, some may consider the risk assessment that supports a particular protection level to be "too conservative" (i.e., it overestimates risk), while others may feel it is "not conservative enough" (i.e., it underestimates risk)."

If the EPA were to focus exclusively on the harmful side of exposure at low doses, while ignoring the beneficial side, then its stated objective (i.e., *"to adequately protect"* health) is likely to be compromised and fails to comply with the DQA. Such a one-sided focus, rather than being benign as the EPA seems to assume, can lead to distorted resource allocations and to regulatory constraints that increase health risk. The issue is that focusing on risk alone provides only part of the tuple that must be considered for socially beneficial decision-making:

{net health risks, net health benefits, economic and social costs and benefits}.

Risk assessments should not knowingly underestimate risks. This agency policy does not give balanced consideration to the health (and economic) consequences from false positives (or over-estimates) as well as from false negatives (or under-estimates) in exposure-response relations. (In passing, some economic analyses have estimated a 10:1 ratio between money spent on false negatives and false positives (Cranor, 1993). Not to account for both types of errors undermines the ability of public and other stakeholders to make well-informed decisions based on full information about the probable consequences of alternative risk management decisions.) While data-driven or judgment-driven probabilities that alternative dose-response models are correct can perhaps appropriately be included in risk assessment calculations, hidden policy and value judgments (e.g., a risk-averse attitude or preferences for certain actions) must not be if the consumers of the risk assessment are to be left free to make their own judgments, relying on the risk assessment only for technical information about the causal relation between alternative actions and their probable consequences. If hidden value judgments and/or preferences for default positions distort risk assessment information, then regulatory science-policy can lead to gross misallocation of scarce resources by recommending actions that are less likely to achieve their stated goals than the assessment suggests.

A somewhat analogous issue is that, as the US EPA states (2004; emphasis and comment added):

"Further, when several parameters are assessed, upper-end values and/or central tendency values are generally combined to generate a (possibly unbiased) risk estimate that falls within the higher end of the population risk range (under specific and often limiting statistical criteria such as homogeneity of the variance, identical distributions, and independence assumptions within an inferential framework in which sample size and other considerations are very important)."

Use of upper-end estimates for a range of risks or exposures, when the Agency is uncertain about the true values, can lead to investments in risk management options that might be rejected if a fuller, more neutral presentation of their probable consequences (uncertainties and all) were used instead. For example, it has previously been concluded that:

In reviewing two dozen cases where reliable before and after cost estimates of environmental and health regulations exist, overestimation of total costs appears to be more common than underestimation. At least for federal rules, this is frequently due to overly pessimistic assessments of future pollution levels and, conversely, overly optimistic forecasts of the regulation's effectiveness (Harrington et al., 1999).

Some investigators have estimated that EPA regulations have caused costs that range from 2.7 million 1990 US dollars for averting a premature statistical death from arsenic/copper smelting, to the benzene (CAA, NESHAP) with 32.9 million 1990 US dollars per statistical premature death averted, to over 92 billion 1990 US dollars per statistical premature death averted for atrazine/alachlor drinking water standards (Sunstein, 2002). While these numbers do not capture all of the benefits from regulating toxic substances (such as illness-days avoided) and while some issues associated with the choice of discount rate are not reflected, nonetheless, it seems plausible that use of default assumptions can encourage relatively large investments that yield relatively slight (or no) real health benefits – not the most effective use of scarce resources to promote public health.

Role of Defaults and Consensus when Data are Unavailable

What are defaults? The US EPA's (2004) reasons that:

> "… default assumptions are generally supported by scientific data and/or scientific consensus. Their use in risk assessments is to allow the risk assessment to proceed when chemical- and/or site-specific data are missing or not useful."

Consistently with decision-theoretic methods, when data are missing (but there is enough evidence to create useful expert elicitations) then experts' opinions can be encoded as prior probabilities or distributions. If not, then sound decision analysis requires acknowledging that relevant data are missing, rather than "allowing the

risk assessment to proceed" without it. Allowing risk analysis to proceed when the data required to assess risks usefully are not available is, at best, a mixed blessing. Stating that more information is needed to confidently assess or bound risks may be preferable. As the US EPA (2004) states:

> "default assumptions utilized in any given risk assessment entail science policy positions or choices … . For example, a change that is considered adverse (i.e., associated with toxicity) in an animal study is assumed to indicate a problem for humans unless data demonstrate otherwise."

These statements do not address the possibility of a hormetic response. If a study correctly indicates a *positive* effect of some exposures on human health, then such effects ought to be included in risk calculations, either as a decrease in risk or as an improvement in the health status, at those exposure levels. Not accounting for this type of risk-reduction benefit can both overestimate the risk from the substance being regulated and overestimate the benefits of reducing exposures. The US EPA (2004) Guidelines rely on the earlier US EPA (US EPA, 1992) guidelines:

> "… that when exposure data or probabilistic simulations are not available, an exposure estimate that lies between the 90th percentile and the maximum exposure in the exposed population be constructed 'by using maximum or near-maximum values for one or more of the most sensitive variables, leaving others at their mean values'".

It is not clear that this is a sensible procedure from a decision-analytic perspective (e.g., that it makes desired outcomes more likely). To the extent that it distorts the numbers that are relied on by management for controlling, reducing or eliminating hazards, it may lead to allocations of resources that do not optimize reductions in (uncertain) risks. The type of statistical and probabilistic analysis used to develop "high end bounding estimates" should be described and compared to alternative representations of uncertainty. The US EPA (2004) asserts that (comments in parenthesis):

> "Where data are sparse and uncertainty great (perhaps including a great number of zero counts), EPA carries out a screening risk assessment that tends to use default assumptions to avoid underestimating risk. These screening assessments typically provide high-end and bounding estimates. Pathways of trivial importance are then eliminated, and the remaining estimates are refined. This approach either demonstrates with minimal effort that no risk is large enough to consider reducing or, if that is not the case, it eliminates further work on refining estimates for pathways or chemicals that are clearly not important."

However, it is not clear that using defaults really does help to assess the (true) risks in a way that improves decisions, based on comparisons that use the same measure of success, such as reduction in QALYs lost per year. Rather, default assumptions may simply replace an informative but uncertain estimate of the true risk with a less informative default number that carries a lower value of information (VOI) for decision-makers. The US EPA's logic can be summarized as follows:

> Great Uncertainty → {Use Default Based on Consensus → Estimate (presumed) Upper Bound Risk(s)}$_{\text{screening RA}}$ → Eliminate Trivial Pathways → Decide if More Complete Analyses Are Required Based on the Magnitude of that Risk → Conduct More Refined Analyses of Risk → Managerial Decision: clean up or other to the level of acceptable risk.

When there is insufficient information, it cannot be decided that a risk is of a trivial magnitude (even if all stakeholders agree to what is trivial) by some deterministic defaults. Consensus-based defaults must overcome common fallacies, long recognized in psychological investigations of heuristic reasoning, as well as cognitive biases on a case-by-case basis. More importantly, those defaults must change as the state of the information changes. An alternative to a default-based approach is to use a decision-theoretic framework with explicit loss functions.

COMMENT

In the environmental statutes that govern the EPA, there appears to be no Congressional command to regulate without sound causal knowledge. In practice, the US EPA must make policy even when causal relations (e.g., dose-response relations) are uncertain and variable across individuals and populations. In this effort, it seeks to find sufficient knowledge to *regulate* environmental risks responsibly ***and*** to withstand legal challenges.

We can also agree that model *uncertainties arise because of gaps in the scientific theory that is required to make predictions on the basis of causal inferences.* (Uncertainties can also arise from other sources, such as missing data, error-prone measurements, and so forth.) In risk assessment, dose-response relations estimated from sample data (and from the diagnostic analyses and corrections associated with well-conducted data analyses) provide a causal model that, together with theoretical insights, can help to support effective policy analysis. An important challenge is that alternative policy outcomes can seldom be tested or observed after a decision has been made, and thus model validation can be impossible except by coupling emissions to exposures via fate, transport and other models.

Model estimation issues raised by the US EPA (2004) as

a) Relationship errors … c) Incompleteness, i.e., exclusion of one or more relevant variables …d) Use of surrogate variables for ones that cannot be measured.

are some aspects of potential model specification errors. Model uncertainty refers to causal model specification and choice of models, following the logic depicted below:

mechanistic knowledge (e.g., physiology, epidemiological results) → theoretical (e.g., bio-statistical) model specification) → data availability on theoretically necessary input and output variables → resulting causal model specification → estimation and results → diagnostic analyses → re-specification and new estimation results → risk management feedback to policy-makers.

Variability concerns the population frequency distribution of relevant individual characteristics at each step of the process just described. Both Bayesian estimation methods as well as classical methods allow analysis of such problems with both uncertainty and variability in the relations between exposures and resulting risks. We concur with the US EPA (2004) that:

Uncertainty can be reduced by further research that supports a model or improves a parameter estimate, but human variation is a reality that can be better characterized, but not reduced by further research.

The preceding discussion supports our main contention that non-linear dose-response should now be included in the portfolio of dose-response models used in regulatory analyses. This allows for a decrease on the reliance by the US EPA on a single default dose-response model. Reasons to include causal models beyond defaults and the LNT model are:

1. In the literature, hormetic dose-response models are now sufficiently well established for such inclusion (Calabrese and Baldwin, 2001; Calabrese and Baldwin, 2003; Ricci et al., 2004),

2. The physiological basis of these models is empirically well-established for a wide variety of end-points

3. The legal basis for such inclusion is well-established

We also concur with this Agency's belief that (emphasis added) (US EPA, 2004):

> "The very heart of risk assessment is the responsibility to use whatever information is at hand or can be generated to produce an estimate, a range, a probability distribution — whatever best expresses the present state of knowledge about the effects of some hazard in some specific setting. To ignore the uncertainty in any process is almost sure to leave critical parts of the process incompletely examined and hence to increase the probability of generating a risk estimate that is incorrect, incomplete, or misleading (NRC, 1994). The NRC (1994) further noted that risk assessments that do not pay sufficient attention to uncertainty are vulnerable to four common, potentially serious pitfalls …" (p. 33)

EPA's approach here appears to be consistent with our proposal to use decision-theoretic models for assessing risky decisions if "use whatever information is at hand or can be generated" is interpreted specifically as: "condition risk estimates on whatever information is at hand or is expected to be worth paying to generate". Inherent to this formulation, updating a model uncertainty decision tree with new information can be done routinely using Bayes' or other updating rules.

We follow Granger (1998) and suggest that "a generalized form of relevance" should be the guide for causal models in risk assessment at low doses. Specifically, "a theory or model should be evaluated in terms of the quality of the decisions that are made based on the theory or model." More specifically, Granger (1998) states:

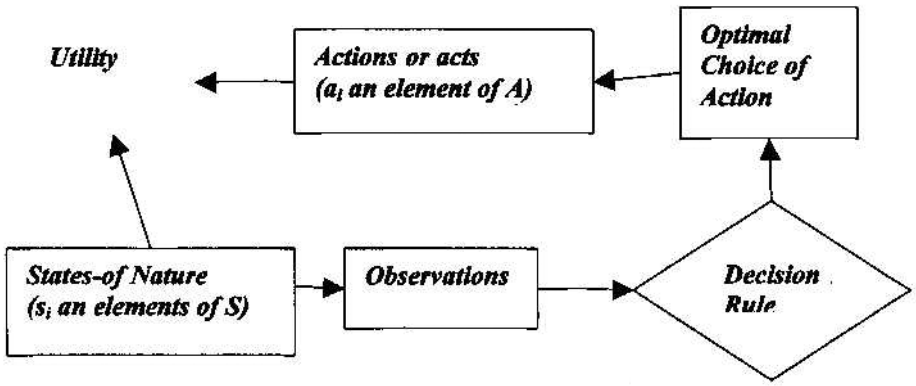
> "It is inevitable that the decisions are made temporally later than the period over which the model was specified and thus the evaluation is … 'post-sample', rather than the goodness-of-fit 'in-sample,' which is now often used. … The in-sample v. out-of-sample performance of the model can be (and usually is) different … ."

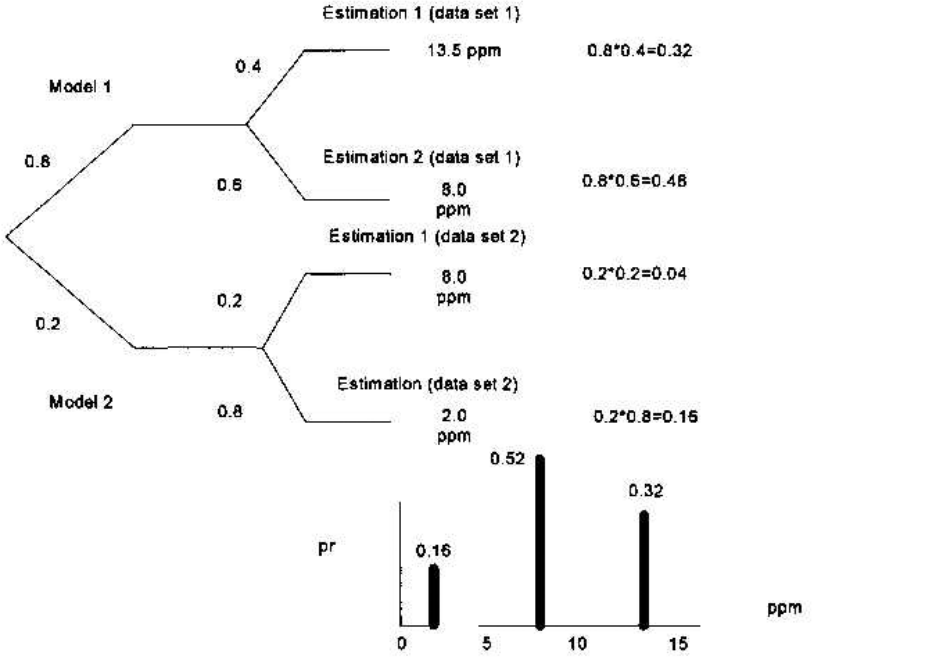
A way to handle "whatever information is at hand or can be generated to produce an estimate" is through decision-theoretic methods, which allow stakeholders and other to weigh alternative models as well as data sets used in estimating losses, within a formal method for assessing both a priori beliefs and experimental (or observational) data sets, while accounting for new results by sequential conditioning on new information. This can eliminate the need for deterministic defaults with the added advantage is that doing so fulfils the US NRC (1994) concerns because it assures transparency and explicability, is consistent with probabilistic reasoning about incomplete as well as complete data and causal models, and is theoretically sound. Moreover, this approach to science-policy in risk assessment seems to fulfill the DQA's requirements relative to the dissemination of scientific information. The decision-theoretic process is depicted below:

The application of this concept is illustrated next, without adding the expected costs and the resulting optimal choice (which, under this example, arises from the decision rule to minimize the expected cost, the payoffs shown earlier):

To illustrate the concept we show a situation where a risk assessor has used two data sets and two models to estimate the tolerable exposures, measured in parts per million, to a toxic agent found in soil. She has used $1*10^{-5}$ as the tolerable risk level, but is unable to determine which of these results is most credible, and thus develops a decision tree. Model 1 is representative of a class of models; Model 2 is representative of an alternative family of models. Given her experience with the substance, its biological effects and knowledge of exposure-response, the decision tree is as follows.

On the basis of these results, she recommends to the risk managers that the most plausible exposure level is 8.0 ppm. Suppose that there is controversy about this recommendation: other degrees of belief can be used to investigate the alternatives and come to a sound conclu-





Distribution of exposures at an individual lifetime tolerable risk level 1/100,000, resulting from fitting two different exposure-response models to two different data sets. ppm is parts per million.

sion. Naturally enough, the sets of data and classes of models (or even each model) can be included in this formal and replicable representation.

Applying this reasoning to hormesis would make immediately clear that probabilistic weights account for the fact that:

1.There are at least two types of hormetic mechanisms,

2. The stimulation mechanism occurs at levels that are relatively small, compared to the response in the controls (e.g., a 30% range),

3. Some physiologically adverse responses (e.g., endocrine disruptors) can confound the understanding of hormetic response, and

4. Alternative dose-response models, such as the LNT model, are included as necessary for the analysis.

Decision-theoretic methods are not biased toward one theory (or data set) or another. Quite the opposite: the role of decision-theoretic models is to show value judg-

ments and degrees of risk aversion to those participating in the decision-making process for reaching a regulatory number, rather than obtaining a number through a consensus process that can be cloudy and only gives the results of deliberations (e.g., a factor of safety is the result of reasoning that is not necessarily consistent with rational decision-making under risk or uncertainty). Measured and replicable results that portray alternative beliefs (in which the intensity of a belief is measure by probabilities) are necessary to the assessment of regulatory choices that result in changes in risk through the allocation of scarce resources. Doing otherwise has the following consequences for modeling (US EPA, 2004), because these:

a) do not allow for optimal weighting of the probabilities and consequences of error. b) … do not permit a reliable comparison of alternative decisions. c) … fail to communicate the range of control options that would be comparable with different assessments of the true state of nature. d) … preclude the opportunity for identifying research initiatives.

Because decision-theoretic criteria (such as elimination of dominated alternatives) provide a theoretically sound rationale for making those choices under both risk and uncertainty, public agencies can now deal with the fact that (US EPA 2004):

> "uncertainty analysis will play a more prominent and formal role in regulatory decision making. For example, OMB's recent revisions to its regulatory analysis guidelines ... state that formal quantitative uncertainty analysis be performed for economic assessment in support of overall regulatory analysis. For major rules involving annual economic effects of $1 billion or more, a formal quantitative analysis of uncertainty is required." (p. 34).

Moreover, decision-theoretic methods contribute to US EPA's (2004) proposal to deal with variability and uncertainty by depicting a stakeholder's summary set of beliefs:

> "The use of sophisticated uncertainty tools also involves substantial issues of science and mathematics … It is not, however, EPA's intent to suggest that full probabilistic models of cancer risks are generally feasible at this time, or that the role of a qualitative presentation of uncertainties should be diminished." (p. 49)

If we understand this attitude, with think that it can have grave consequences for environmental policy because:

1. It is myopic (and circumvents the admirable research done by and for the US EPA), because Bayesian (and other probabilistic methods) are now sufficiently well established in the peer-reviewed literature that their use can withstand the admissibility standard of *Daubert* and its line of cases dealing with the admissibility of evidence,

2. It is inconsistent with advancing the state-of-the-art regarding regulatory science and law,

3. It is inconsistent with the need to avoid making "conservative" assumptions,

4. It continues to promote default reasoning that is increasingly unwarranted in most of the risk analyses conducted using the US EPA methods and numbers,

5. It is inconsistent with the DQA.

CONCLUSION

We gave a limited discussion of some of the issues that affect science-policy at the intersection between science and administrative law, from the vantage point of current US EPA policy (2004). We find that the US EPA limits its scientific analyses by an unwarranted reliance on default causal reasoning and thus biases the discussion and understanding of the science underpinning its risk assessments. The implications of the US EPA approach conflicts with scientific state-of-the-art as well as with having to use "sound" statistical methods in its risk assessments. This result can be deleterious to society's health because it results in:

1. Causing society to spend potentially very large sums of money for comparatively little benefit (measured by a decrease in health risk), and
2. Denial of health benefits by regulating chemical and other agents at low doses, in a sub-interval between a NOAEL and some suitable lower dose or exposure level.

Effective decision-making (e.g., finding undominated or expected utility-maximizing alternatives) requires conditioning on all relevant (Value Of Information > 0) information and allowing for multiple models that are consistent with data (as in BMA). Nowadays, those models should include U- or J-shaped dose-response curves as possibilities. Allowing for these possibilities leads to better decisions, which are almost surely superior to a priori exclusions. We believe that it is incumbent upon a regulatory agency to fill the gap between Congress and the courts with a method that is truly consistent with *the best possible science*. To do otherwise is a disservice to society because relinquishing this function incorrectly passes the responsibility to the courts, which are often unable to deal with complex and often changing heterogeneous and uncertain scientific evidence, and causation. The method requires a full description of choices, states of nature, and pay-offs, and it must be replicable. Using such a method accounts not only for changing and complex information, but also provides uniformity of analysis based on probabilistic measures of uncertainty.

NOTES

1. The administrative procedures that follow under the Administrative Procedure Act are either "rule-making" or "adjudica-

tive." Each can have formal (on the record) or informal proceedings. APA § 651(5)-(9).

2. We suggest a new issue for risk assessment, in the wake of the DQA, due to the distance between defaults and the state-of-the-art science. Under *Hazel-Atlas Glass Co.* v. *Hartford-Empire*, 322 U.S. 238 (1944), a US Supreme Court case) and more current cases (dealing with fraudulent introduction of evidence by officers of the court, such as the attorneys for either party), agencies may run the risk of committing such fraud. The issue is that introducing evidence geared toward supporting a position, while disregarding an alternative, equally or even superior, scientific theory, prevents the reviewing court from being able to balance evidence and reach a fair and equitable resolution to the controversy. It appears possible that not using appropriate modern statistical methods for analysis, while knowing that such methods exist, may fall within the *Hazel-Atlas* line of cases.

3. (42 U.S.C. § 300g-1(b)(3)(A)).

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