UNCERTAINTY IN HEALTH RISK ANALYSIS

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Summary

This paper discusses several quantitative issues that arise in the analysis of health risks, beginning with principles such as *de minimis* and zero-risk. The paper also provides a probabilistic definition of risk in terms of hazard, context, consequence, magnitude, and uncertainty. The example relies on this definition to investigate, through sensitivity analysis, the effect that uncertainty has on the results obtained. The results, from a case study based on waterborne total arsenic, show that the choice of dose—response functions causes more uncertainty than any other component of risk analysis. Chemical carcinogenesis provides the basis for discussing inability to know as well as uncertainty. The conclusion is that risk analysis keeps uncertainty and inability to know separate; through this function, it provides a much needed method to present information to decision makers and the public.

Introduction

Health risks can be present long before they are recognized. Often, delaying an action to control risks shrouded by uncertainty and lack of knowledge leaves society open to the small probability of great future harm. Alternatively, an unduly quick response can create lasting false impressions or be counterproductive. These two aspects are asymmetric, leading to an abundance of policy-laden affirmations; for example, environmental and safety statutes contain a variety of prescriptions about what can and cannot be done to regulate risk. Those prescriptions range from "zero-risk", the banning of an additive found to be a carcinogen, to the requirement of cost—benefit analysis before issuing regulations [1]. Moreover, environmental and safety statutes contain well-established legal wording: "reasonably practicable", "significant", and "adequate" that, when dealing with risk assessment at low doses, create additional uncertainty [2]. Vague wording has led to judicial reviews of what these modifiers precisely meant. The tension between "zero risk" and what is "reasonably practicable" is powerful simply because absolute safety is a "chimera". Regardless of the policy affirmations, health risks must be quantitatively determined before actions are taken. Events, probabilities, the magnitude of each consequence, and choice of

dose—response functions are intrinsic factors to such determinations. *De minimis*, as an acceptable risk, for example 10^{-6} individual lifetime excess risk of incurring a specific cancer, is a policy consideration which requires quantitative analysis of risks. In the wake of conflicting principles and conflicting statutory language regulatory efforts differ in their approach towards regulating risk; they, as the statutes, range from requiring zero-risk to benefit—cost analysis.

Whether to wait for irrefutable evidence about the causes leading to adverse health effects, or to take what may be a conservative course of action through imposing a high "factor of safety" to an experimental dose found to be toxic, is a policy question. In risk analysis, uncertain and unknowable scientific facts mix with policy propelling the need for unifying scientific issues; or attempt is directed to this end.

We assume that scientific analysis and evaluation form risk assessment. These two aspects are separable [3—5]. This is a necessary, but difficult, step because the analysis itself has intrinsic evaluative aspects. For example, the choice of a confidence level on the estimation of a dose—response function may be imposed by policy *fiat*.

We discuss how risk analysis relies on data, formulae, and models linked to measure risk. Those data and models form a system for keeping track of the hazards, their context, the consequences, and the associated uncertainty. A plausible system, shown by a parsimonious choice of interconnected elements, is

$$Q \to F \to M \to C \to U \to D—R \to E \tag{1}$$

where Q: electric energy output (MW(e)-year), F: fuel (tonne/year), M: emissions (e.g., stack emissions, in pounds of total As/year), C: concentrations (e.g., ppm), U: uptake (e.g., soil, plants, lower animals), D: biological doses (dose, duration of exposure, biochemical transformations within the human body), R: dose—response function (e.g., incidence of skin cancers, a function of D), and E: consequences over the population (e.g., total excess cancers).

The first two elements result from the production of electric energy and in the release of hazardous substances (e.g., pounds of As/hour). Those releases are transformed into concentrations through models that describe and predict the fate of pollutants in air, soil, and water. The concentrations represent the incremental exposure, from producing those Q (MW(e)-year, over background. Coupled with uptake, dose—response functions, and demographic data, system (1) shown above yields the total excess risk, for those at risk, from exposure to total As. Spatial distributions affect C, U, D, and E. Normally, E is a lumped variable, Q can be a point or an areal source, and F and M are source-specific. This system is the "road-map" used to discuss uncertainty, inability to know, and the example. We begin with defining risk and its elements.

Risk: Its components

We describe "risk" as a function of three elements: cause of consequence; consequence; and uncertainty.

The cause of a consequence contains hazard and context. We distinguish between hazard, which exists in the abstract, and context, which identifies how and where the hazard might occur (Table 1). An example of a hazard is the production of a specific amount, Q MW(e)-year of energy, which leads to adverse consequences; for instance, delayed deaths [6—14]. Those consequences can be defined if the context within which energy production occurs is known. Examples of context are the type of power plant and the power pool in which it operates.

The choice of consequences depends on the purpose of the analysis. An example of a class of events may consist of specific mechanical failures, within a power plant, such that energy cannot be produced at a certain instant,

TABLE 1

Components used in describing risk

Element	Description
Hazard[a], h	This is the source or origin of bad consequences. For instance, the production of Q MW(e)-year of electricity, the extraction of C tonnes of coal, and an earthquake are hazards.
Context[a], c	It includes the information available and relevant to define how the hazard occurs. For example, a rural coal-burning power plant and an urban oil-burning power plant are different contexts for the same hazard, the production of Q MW(e)-year by the same plant.
Consequences, E	They include all effects relevant to the analysis, from health effects on humans to effects on vegetation, and socio-economic consequences. The *status quo* may be the baseline.
Uncertainty, U	Data variability, model underspecification, and lack of knowledge impose a probabilistic approach to show their effect on the results of any risk analysis.
Severity, s	It is the ranking of consequences relative to a maximum level of damage. The "maximum level of damage" may be delayed death; actual choice depends on the objective of the analysis (and judgment).
Magnitude, x	It is a number describing the extent of a consequence of given severity. Thus, the number of deaths and the number of illnesses indicate the magnitude of a consequence.

[a] Although there may be a fairly long chain of causality, it is, in principle and in practice, possible to reduce the number of components of the system being studied. We have done so in system (1).

t. This class of events should be logically complete; thus, if $p(e_i)$ is the probability that the *i*th event occurs, then

$$\sum_{i \in I} P(e_i) = 1 \tag{2}$$

where the summation is taken over all events within the class considered. We assume that consequences and classes of events can be used interchangeably; we let the ensemble of the consequences be

$$E = \{ e_1, e_2, \ldots, e_n \} \tag{3}$$

We can define risk, R, as a set formed by the hazard, h, the context, c, the class of events, E, and uncertainty, u

$$R = \{ h,c,E,u \} \tag{4}$$

Uncertainty pervades h, c, and E; thus

$$R = \{ h,c,E,p(h,c,e) \} \tag{5}$$

where $p(h,c,e)$ is the probability of the hazard, h, context, c, and consequence, e. Consequences are defined by type, or severity (e.g., a prompt death may be weighted differently than a delayed death), and magnitude (e.g., the number of prompt deaths). The type of consequence, s, and the magnitude, x (zero or positive real number), can be shown as an ordered pair

$$e = (s,x) \tag{6}$$

Generally, h, c, and E depend on time; this dependency can be shown in the argument of the probability $p(h,c,E,t)$. Spatial dependence can be shown similarly.

The analysis of health risks is based on setting one (or more) objective(s); for example, minimize societal health risks, or a subset of risks (i.e., total prompt deaths, total illnesses, and so on). Clearly, the measure of the consequences is the magnitude; it can be measured by the number of total prompt deaths. The purpose of the analysis is to calculate that number and its uncertainty. An often used criterion is the expected value of the magnitude of a consequence [15–17].

A more plausible and general approach to portray the magnitude of a consequence is the inverse of the cumulative frequency distribution of the magnitude. We rewrite eqn. (5) as

$$R = \{ h,c,E,p(h,c,e,t) \} \tag{7}$$

Since $E = \{ e_1, \ldots, e_n \}$ it follows that

$$R = \{ h,c,E,p(h,c,t,e_1, \ldots, e_n) \} \tag{8}$$

If, for all i and j, a consequence e_i does not depend on e_j, then

$$p(h,c,t,e_1, \ldots, e_n) = p(h,c,t,e_1)p(h,c,t,e_2) \ldots (p(h,c,t,e_n) \tag{9}$$

The right-hand side of eqn. (9) contains e_i, which is characterized by severity s_i (e.g., accidental prompt fatalities) and magnitude x_i (the number of accidental prompt fatilities) [11, 15, 18—22]. $p(h,c,t,s,x)$ can be used to write the probability

$$p_T(h,c,s,x) = \int_{t_0}^{t_0 +T} p(h,c,t,s_i,x_i)\, dt \tag{10}$$

that, in the time interval t_0 to T, with t_0 the initial time, there is a situation characterized by (h,c) and a consequence s_i of magnitude x_i. Applying the multiplicative property

$$p_T(h,c,s_i,x_i) = p_T(h,c)p_T(s_i,x_i|h,c) \tag{11}$$

where $p_T(s_i,x_i|h,c)$ is the probability of occurrence of magnitude x_i, conditional on the hazard, h, context, c, and consequence, s_i, in the temporal interval T, beginning at time t_0. The conditional probability on h, c, and s_i, that the magnitude is less than some integer number N (e.g., the number of prompt fatalities) is

$$F_T(s_i,N|h,c) = \sum_{k=0}^{N-1} p_T(s_i,k|h,c) \tag{12}$$

When the magnitude is continuous (e.g., delayed deaths, prompt deaths), the probability density function with respect to the real-valued variable x, $p_T(x|h,c)dx$, yields the conditional probability that the magnitude be within x and $x + dx$, given the time interval t_0, T.

The probability that the magnitude is less than or equal to some value of x is

$$F_T(s_i,x|h,c) = \int_0^x p_T(s_i,\epsilon|h,c)d\epsilon \tag{13}$$

F_T is the cumulative distribution of the variable $x(0,N)$, monotonically increasing, with $F_T(0|h,c) = 0$, unless $P_T(0|h,c) \neq 0$, and $F_T(\infty|h,c) = 1$. The function

$$R_T(s_i,x|h,c) = 1 - F_T(s_i,x|h,c) \tag{14}$$

is the complement of F_T. When $R_T(s_i,x|h,c)$ and $p_T(h,c)$ are multiplied, the product is the probability that an event characterized by an hazard, h, context, c, and consequence, s, the magnitude of which is greater than or equal to x, occurs in the time interval t_0, T

$$R_{h,c,s}(x) = p_T(h,c)R_T(s_i,x|h,c) \tag{15}$$

Most studies account for uncertainty through the choice of confidence level. This is justified by statistical criteria, tradition, or by the objective of further reducing the risk to those who are especially sensitive.

In this paper, the example captures uncertainty by adopting optimal,

nominal and pessimistic values through sensitivity analysis. Hence, the example does not use the definitions developed above specifically. Nevertheless, the reader can profit from the analysis presented here as it provides a succinct way for discussing health risks.

Sources of uncertainty

The analysis of health risks is affected by variability (e.g., differences among assumptions about the technology under study) and by uncertainty (e.g., data or models) [23]. At least two forms of uncertainty characterize such analysis: scientific and existential. The former includes the uncertainty in data or models, but it extends to scientific theories that link causes and effects; the latter is imposed by the realities of life.

Our concern is with scientific uncertainty and the limited ability to know the causal mechanisms necessary to accurately analyze health risks. We take chemical carcinogenesis; the issues addressed are: causality at low doses and dose—response functions.

In determining what "safe" levels of contaminants in drinking water might be, the U.S. National Academy of Science (NAS) [24] found that it is generally impossible to determine whether, at low doses, a contaminant deemed to cause carcinogenesis could have a threshold below which an adverse effect would not occur. Thus, for chemical carcinogens affecting somatic cells, the NAS called for risk analysis with the following principles [24]:

(1) Effects in animals, properly qualified, are applicable to man.
(2) Methods do not now exist to establish a threshold for long-term effects of toxic agents.
(3) Exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man.
(4) Materials should be assessed in terms of human risk, rather than as "safe" or "unsafe."

As the NAS notes, these principles run into the current inability to know the mechanisms of cancer induction.

A plausible policy question is: Given a target level of excess individual lifetime incidence of cancer (for example, 10^{-6}), what is the dose (i.e., the concentration) that can be considered appropriate as an environmental standard? This is a seemingly innocuous question; if 10^{-6} were chosen, the environmental standard would be straightforward to determine. Unfortunately, the question is fraught with difficulties. These revolve about several factors: cancer induction [25—29], actual (biologically effective) dose [30—32], extrapolation of potency from animal studies to humans [33—36], choice of dose—response functions [37, 38], and epidemiology [39, 40]. Dose—response functions mathematically describe the incidence (or other measure) of the adverse effect, as a function of the dose causing that effect [39, 41]. Those functions, commonly applied to the analysis of both public and occu-

TABLE 2

Dose–response functions commonly found in risk assessment of carcinogens

Dose–response functions[a,b]	Discussion on parameters	Remarks
(1) $p(D) = 1 - \exp(-kD)$ (Ref. [42])	$k > 0$. The proportion unaffected is $\exp(-kD)$. The reaction rate is first order in the concentration of the pollutant. The exposure rate is constant, over some period of time t, i.e., $p(D) = 1 - \exp(-\alpha t D)$; $\alpha \geq 0$.	Single-hit model; a single hit causes irreversible damage to DNA leading to tumor. At low doses, the function is linear; once the biological target is hit, the process leading to tumor continues independently of dose.
(2) $p(D) = 1/\Gamma(k) \int_0^{\lambda D} u^{k-1} \exp(-u) du$ (Refs. [43, 44])	Q is the gamma function; for k integer $\Gamma = k!$ Where $k = 1$, $P(D) = 1 - \exp(-kD)$ When $k > 1$ (2) is convex; $k < 1$ (2) is concave. At low doses $p(D) \approx (\lambda D)^k / \Gamma(k)$.	Gamma multihit model, k shows the sensitivity of the biological unit to insult, i.e., the number of hits required for irreversible damage.
(3) $p(D,t) = 1 - \exp(-g(D)h(t))$ (Refs. 42, 45, 46)	$g(D) = \prod_{i=1}^{k} (\alpha_i + \beta_i D)$; t is time, $\alpha_i > 0$ and $\beta_i > 0$; $h(t) = \int_{\Delta t} f(t-u) u^{k-1} du$, where $f(t)$ is the density of time for cancer induction.	This is the multistage model. The incidence of a tumor, given dose D, at age t, requires k stages before the tumor is initiated in a single line of cells. $h(t)$, in the nonparametric multistage function, is "an arbitrary increasing function."
(4) $p(D) = \Phi[(x-\mu)/\sigma] = \Phi(\alpha + \beta \log_{10} D)$ (Ref. [47])	$\alpha = -\mu/\sigma; \beta = \sigma^{-1}; \Phi$ is the cumulative normal distribution function.	Probit model; at low doses the response decreases rapidly.
(5) $p(D) = 1 - \exp(-\alpha d^k t^n)$	$a, k, n < 0$.	Distribution of individual tolerances to the carcinogen. Duration of exposure, t, is included.

[a] $p(D)$ is the proportion affected, D is the dose per unit dose.
[b] For dose–response functions used in radiation carcinogenesis, see Refs. [48, 49].

pational health risks, require accurate understanding of causation at low doses (Table 2).

The NAS [31] indicates that, though earlier its committee had endorsed the multistage model to extrapolate risks from waterborne chemicals, it is now "premature ... to recommend any single approach" for extrapolation, leaving the choice of the model or models to the researchers. But, although several functions may be statistically plausible at high doses, at low doses this is not the case [42, 49]. As a result, large uncertainty arises [50]. We show such uncertainty in the example that follows these discussions.

Quantal functions provide information on whether the disease is present or not. Time-to-response functions account for the probability of observing a tumor at some point in time. Krewski et al. [51] compare time-to-response functions with quantal models and find that, for the multistage Weibull compared with the multistage, the time-to-response information "... will not result in estimates of risk in the low dose region that are substantially more precise than those based on quantal data ...". These authors examine the multistage Weibull, the multistage (non parametric) and the Hartley—Sielken time-to-response functions; as well as the probit, Weibull, multistage and the linear—quadratic quantal models. The findings indicate that the point estimates of risk were generally "highly variable". For example, the three time-to-tumor models yielded "point estimates of risk in the low dose region (that) were highly variable, with the actual risk at the VSD (virtually safe dose) often being a factor of 1000 or more greater than the target risk of 10^{-5} ...". The difference in results between quantal and time-to-occurrence models is about a factor of 10.

Whether a threshold exists or not affects the choice of dose—response functions and causes much debate in health risk analysis. The key arguments for no-threshold are based on the hypothesis that a single insult (hit) to the DNA (for instance, the change to a DNA nucleotide which causes a point mutation) leads to a self-replicating malignant cell which produces cancer. Exposure to a carcinogen, when the alteration of a cell line is already ongoing, leads to linearity at low doses [38]. Moreover, when the single cell is the "biologic unit at risk", if initiation is a threshold phenomenon and there is a random distribution of thresholds (in dose), then "low dose response on the whole tissue over background will be approximately linear" [38].

The arguments for a threshold principally involve repair mechanisms, the existence of bodily defenses, the apparently different mechanisms through which some neoplasms are induced by hormones and other chemicals, and detoxification. A closely related question is: What is the actual (biochemically active) dose causing the irreversible damage?

Some chemicals undergo metabolic changes to form reactive, and thus damaging, metabolites. For example, B(α)P can be activated, through epoxidation, via the cytochrome P450 system and catalysis, to form a dihydrodiol epoxide, a likely carcinogen. B(α)P forms irreversible chemical bonds in the liver without "... initiating or inducing liver cancer in adult animals" [26].

Other chemicals, e.g., bis(chloromethyl) ether, do not appear to need metabolic conversion to a reactive form. Generally, the role of chemical bonds in initiating cancer is not elucidated. Nevertheless, for most chemical carcinogens, what "dose" is cannot be ascertained without biochemical information [52].

Weisburger [32] compares carcinogenic respose by 10 animal species, trout, and man to exposure to N-2-fluorenylacetamide (2AAF). In human and monkey, the response is questionable. In cat, rabbit, chicken, dog, hamster, and rat, the response is positive; and in guinea pig, mouse, and steppe lemming, the response is negative. Rainbow trout also has negative response. The author also investigates the urinary excretion of three metabolites of 2AAF, N-OH-FAA, 7-OH-FAA, and 5-OH-FAA, and finds that monkeys excrete "appreciable amounts" of N-OH-FAA, but they do not show a positive response. X/GF mice, also resistant to the carcinogenic effect of 2FAA, excrete N-OH-FAA in quantities relatively close to those excreted by mice which are susceptible to 2AAF-induced cancer.

Animal tests are used to relate carcinogenic potency of a specific chemical from animals to man. There are attempts to account for metabolic differences between species: this is the case for such conversions as mg/m^2 body surface per day or mg/kg body weight per lifetime. There is uncertainty here as well. As Crump and Howe [53] note: "If low dose human risks are estimates from rat data using a linear model, then the mg/kg/lifetime procedure yields human risks which are 12.5 times larger than would be obtained by the ppm procedure."

The sample size required to detect an effect at low doses is necessarily large. For example, if the excess risk is proportional to dose, and if an exposed group of 1000 individuals is required to estimate the excess risk from 100 Rad, then about 10^5 individuals will be required for 10 Rad and 10^6 for 1 Rad [49].

In the next section, we show an example through which health risks from an emitting arsenic from a 500 MW(e) power plant are analyzed [54].

Case study

We briefly discuss here an environmental case study described in detail in Ref. [54], developed by RAND for EPRI. It involved a hypothetical coal-fired (F) power plant, where Q equals 500 MW(e); its context (c): the generation of base capacity, sited near a river. The analysis addressed the chronic health risks. Thus, E is skin cancer, which results from direct ingestion of drinking water containing arsenic emitted from the plant. The surface water model SERATRA [55] was used to generate steady-state transport of arsenic in sand, silt, clay, and dissolved arsenic. This model generates C, given M. Epidemiologic data [56, 57] based on exposure of a Taiwanese subpopulation to arsenic in the water supply, were used to determine E, its severity and magnitude (s,x): the human incidence of skin cancer.

The complexity of the case study prevented direct use of the analytical framework, eqns. (2)–(15), developed earlier in this paper. Nevertheless, an initial attempt to account for paucity of data and limited ability to know (u) was made by resorting to uncertainty analysis. This approach was primarily dictated by the overall complexity of the scientific and engineering factors, and their relationships, as shown in system (1). No compromise could be made there; adding probabilistic treatment of the uncertainty throughout each component would decrease the acceptability of the method by the user. Thus, although certain numerical methods could, in principle, be applied to capture the uncertainty, the simpler approach was preferred. The complexity of coupling several models, as indicated in system (1), arises from the number of inputs and outputs associated with each model and from the number of models that could conceivably be used in the analysis. Uncertainty was approached through single-parameter sensitivity analysis or through varying two parameters at the same time. Although it is, in principle, possible but in practice quite difficult to vary all parameters, the practical bound is $(n-1)!$, where n is the number of parameters.

The inability to know how cancer is induced is approached by selecting plausible dose–response functions, and using these functions in the analysis. Although this approach is "brute force", it nevertheless allows the researcher to better grasp the effect of inability to know. Uncertainty is not shown, although it can be portrayed as a result of statistical estimation. Keeping with the sensitivity analysis approach, the estimated parameters are also subject to variation, single and coupled, to assess their impact on the results.

Various dose–response models, D–R, were employed in the analysis. The calculation of excess cancer risk from exposure to arsenic is based on the assumption of linear pharmacokinetics; dose, from exposure, is proportional to tissue target concentrations and to steady-state concentrations of arsenic. The constant of proportionality is a function sorption, metabolism, and excretion for each species from which cancer data are obtained. These phenomena are approximated by assuming proportionality between the concentration of arsenic in the medium (air and water) and average intake rates, which are species-specific. These assumptions lead to the standard dose; the intake paths considered are ingestion, inhalation, and dermal contact. In this case, there is a single species: the human being. Thus, no interspecies comparisons are necessary. Other assumptions are: (a) kidney clearance is a scalar of body weight; (b) mass of food ingested is proportional to caloric need per day and, thus, to O_2 uptake per day; (c) skin adsorption is proportional to skin area; and, (d) inhalation is proportional to body weight to the 2/3 power, the target tissue concentrations can be derived. These are: for ingestion, ppm by weight; for inhalation, mg/m^3; and, for dermal absorption, ppm by weight.

Four dose–response functions were used: the one-hit, the multihit, the probit, and the Weibull. The functions were statistically parameterized, using the Tseng data, to obtain estimates of the coefficients.

Nominal, or best-guess, values for all parameters and input were used to

calculate the total lifetime cases of cancer, in the regional population, caused by exposure to environmental arsenic levels, minus the cases associated with background arsenic exposure. The background arsenic levels included consumption of arsenic in food products and ingestion of water.

Two different values of time of exposure, in the dose—response models, were used to bracket the expected number of skin cancers. First, exposure time was set equal to the expected operating time of the power plant (35 years), with the assumption that no excess cases attributable to emissions by the power plant would occur after this time. This assumption can underestimate the actual number of excess cases because of latency; individuals are still at risk beyond the end of plant operation and can develop cancer, although at a lower rate than likely under continued exposure. Therefore, in the second case, the expected human lifetime (72 years), was used to provide an upper bound. These assumptions were necessary because no epidemiological data were available describing the occurrence of arsenical skin cancer, after a cut-off in the exposure. The results for the alternative cases for both exposure periods are shown in Table 3.

TABLE 3

Total excess arsenic-induced cancers, plant lifetime and human lifetime (nominal case)[a]

Period of time	Dose—response function			
	One-hit	Multihit	Probit	Weibull
Plant lifetime (35 years)	0.123	0.1277	0.00164	0.0202
Human lifetime (72 years)	0.252	0.0364	0.00337	0.3310

[a] Based on Tseng et al. [56, 57]. The probability from background exposure is estimated to be zero.

A sensitivity analysis indicated plausible bounds about the magnitude of the cancer risks resulting from exposure to arsenic. As expected, the maximum uncertainty arises from the choice of dose—response functions; for example, risks vary from approximately a factor of 10^6 for the multihit function, to a factor of 10^3 for the single-hit function. The probit functions yielded approximately zero excess cancer risk. It can be readily seen than exposure to total As can cause, under the use of the single-hit model, only a fractional cancer.

Conclusions

Most technological activities cause occupational and public health impacts. Risk is defined to be a function of four elements: hazard, context, consequence, and uncertainty; the definition is formalized through a proba-

bilistic approach. Several conclusions can be drawn. First, the choice of a criterion, such as the expected value, does not suffice to portray health risks; more than one criterion may be useful to the assessor. In this case, the cumulative distribution is a more useful method; this approach can be readily extended to several measures of risk. Nevertheless, there is no unique measure of risk; each depends on the stated objective of the analysis. Third, it is necessary to account for uncertainty and ability to know. In an example from chemical carcinogenesis, it becomes clear that inability to know imposes an uneasy communion between science and policy. The case study described here is a practical example of uncertainty and inability to know applied to carcinogenic risk. Risk analysis identifies how and where, in an analysis, uncertainty occurs and its effect on decision making. Thus, the significance of risk, *de minimis* risks and other concepts can be looked at independently of the policy framework within which they are cast. More generally, risk analysis is a useful tool for energy and environmental analyses since it provides information to the policy and decision makers, research planners, and to the public. If developed further, risk analysis will provide information on the attribution of risk among producing activities, a more accurate measure of risk, and a means for enhancing the evaluation and management of technologies that provide energy.

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