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# QUANTITATIVE RISK ASSESSMENT OF ENVIRONMENTAL HAZARDS[1]

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## INTRODUCTION

### *Promises of Quantitative Risk Assessment*

Important decisions regarding public health may involve economic costs of millions or even billions of dollars as well as human costs not comfortably measurable in dollars. No one would want such decisions to be made blindly, without an understanding of the magnitude of the health problem under consideration.

In relatively simple cases, a decision can be made with a qualitative assessment of risk—a subjective evaluation of the likelihood that any one person will be affected or of the total number of people that might be affected. But if we are trying to decide about controls on toxic shock syndrome or a thalidomide analogue or saccharin or radiation from nuclear waste depositories, it is not nearly so evident where an investment in risk reduction will be most effective, because it is not obvious how many people might be affected annually with no controls. *Quantitative* risk assessment is intended to help make such decisions more rationally.

A committee of the National Research Council (33) has recently described risk assessment as the "use of the factual base to define the health effects of exposures of individuals or populations to hazardous materials and situations." Quantitative risk assessment holds out the hope of being able to manipulate the factual base so as to describe the degree of risk that various classes of people face and how many people overall might experience a health effect attributable

[1]The views expressed in this review are those of the author and do not necessarily reflect those of the National Academy of Sciences.



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to such materials and situations. If a reasonably accurate estimate of these risks could be produced, it would be much easier for a person to decide whether or not to undertake an activity or for the government to decide on behalf of society whether a product was too dangerous to be allowed on the market.

This promise of rational decision making is the rationale for further development and use of quantitative risk assessment (21).

## *The Failings of Quantitative Risk Assessment*

Critics of quantitative risk assessment, however, assert that such hopes appear vain in the face of all its difficulties. For example, do we know what conditions are necessary in addition to the use of super-absorbent tampons to produce toxic shock syndrome? What evidence is there that the analogue is enough like thalidomide to have its devastating effect? How different are those Canadian rats from US men and women, and are those huge intakes of saccharin relevant for humans? What is the chain of events that would release radioactivity from the nuclear waste depository, and how likely is each event? What is the consequence of exposure to two or more interacting hazards? Are some people much more susceptible than others?

These questions can be answered, if at all, only with substantial uncertainty. One assessment of saccharin risks (28) estimated the number of cancers expected to arise annually throughout the US from the projected use of saccharin. The estimates ranged from 0.007 to 3640, a difference of nearly seven orders of magnitude. And at low doses saccharin may produce no effects at all; that is, the risk may be zero. Yet users of risk assessments may focus on the central estimates and forget the range of uncertainty.

## *A "Science" that Cannot Be Validated*

The results of quantitative risk assessment—a theoretical exercise—may not be subject to validation by observation. In most disciplines called "scientific," one can make a prediction that can later be confirmed or denied by experimentation in the laboratory or observation in the field.

The predictions of quantitative risk assessment, however, pertain to the number of cases of disease or injury in a defined population exposed to some risky agent or activity. Only in rare cases can these predictions be validated by direct observation. There are several reasons.

1. If the risk estimates are high, then society may act to reduce them, thus spoiling the "experiment" of continuing to live with the risks.

2. Health effects are often not realized until many years after the exposure to the hazardous activity or agent. To analyze the results and eliminate alternative explanations over such a long period may prove impossible.

3. The risks are often quite low (relative to those of smoking, say). If 1000 excess deaths are widely distributed in a population of nearly a quarter billion,

it may be impossible to detect the excess with any reasonable level of statistical significance by any known epidemiologic technique. Land (19) has demonstrated the enormous number of observations needed to detect the presumed excess of breast cancer from 1 rad of x-ray or gamma radiation received at 35 years of age. Both the National Research Council (37) and Erdreich (10) have analyzed epidemiologic studies of ingested asbestos and shown them to be essentially incapable of detecting the estimated risks.

Finally, validation can usually be done only in a statistical sense. If someone develops lung cancer, it may have developed "spontaneously" in the absence of the presumed hazardous agent. Even though an observed effect is plausibly related to the suspect agent, it is not necessarily caused by that agent, because there may be other possible causes. For the more common health effects with several possible causes, the attribution of cause is extremely difficult if not impossible.



## *Quantitative Risk Assessment Compared with Alternative Decision Processes*

In spite of the difficulties discussed above, quantitative risk assessment is useful in many situations involving decisions about risk, which will be made whether or not quantitative risk assessment enters the process (31). (The "no action" alternative is also a decision.)

Most decisions about risks depend on the magnitude of the risk, in terms of the number of people affected or the severity of the effect, especially when the choice is among alternatives that all carry some risk. The most obvious exceptions to this rule involve deciding not to take an unnecessary risk, however small. But many situations entail a trade-off between risk and some benefit of the hazardous activity or agent. A risky product may be more desirable or cheaper than a less risky one; an industry may be more efficient and profitable if the more risky process is used; a medical procedure may be more effective with the more risky drug; a food may be less likely to produce botulin toxin if a potentially carcinogenic preservative is added and no other is available. Although these benefits may accrue to people other than those taking the risks (22, 44), the magnitude of the risks seems important in any ethical framework for decision making (16). Subjective decision processes implicitly estimate these magnitudes; quantitative risk assessment estimates them and their uncertainties explicitly.

Therefore, quantitative risk assessment should be useful unless it can be shown to have counterproductive effects on the decision process, such as (*a*) suggesting too much certainty (by ignoring or underestimating uncertainty) or (*b*) paralyzing action by revealing how uncertain the factual base really is.

In the past, risk assessors all too frequently ignored the analysis of uncertainty, or, like most people, underestimated the magnitude of uncertainties (48).

The Environmental Protection Agency recently asked the citizens of Tacoma, Washington to decide on the trade-off between jobs and the risks of arsenic exposure from the local ASARCO plant. At least in the popular press (2), the risk estimates were presented as reasonably firm. The citizens voted for an emissions limit that was higher than the EPA might have required, but too low for the plant management to accept; the plant closed. One danger of too much confidence in risk assessment is that an unlikely but serious risk will be ignored, when traditional subjective analysis may have included it. But the scientific literature is now full of cautionary statements regarding uncertainty and its analysis. In the program of the 1984 annual meeting of the Society for Risk Analysis, 46 of 116 abstract titles include or imply the word uncertainty.

The possibility that explicit uncertainty may paralyze action is more vexing and needs to be studied by behavioral scientists and possibly by philosophers. By making uncertainty too explicit, it becomes unnervingly clear to people on both sides of a decision how shaky the decision really is. Too many times, the proper decision is quite different at the opposite ends of the range of uncertainty. Thus both sides can find support for their positions, and the supposedly neutral decision makers may find it more difficult to act firmly, because now they know how wrong their decisions could be. The solution is in better techniques of risk management, not in ignoring the utility of what quantitative risk assessment can contribute.



## TERMINOLOGY OF RISK

One of the problems of risk assessment is that the language and terminology of risk assessment has not become uniform and settled. In this section I attempt to define some of the terms used.

A *hazard* is inherent to the agent or activity that causes a problem. For example, asbestos, saccharin, and ethylene dibromide are hazardous environmental *agents,* and nuclear waste disposal, liquefied natural gas storage, and synthetic fuel development are hazardous *activities. Hazard identification* is "the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition" (34).

The results of exposure to these hazards are *effects,* and *risk* is a general term for any way of expressing the probability of observing those effects. For example, the risk of dying of lung cancer (the effect) for a man who smokes two packs per day for 50 years (the hazard) is about one in nine (45). This means that of nine otherwise similar and typical men who smoke that much, one will die of lung cancer and the others will die of something else.

### *Lifetime and Annual Risks*

The risk of lung cancer described above was a lifetime risk. Because everyone dies of something, lifetime risks of fatal effects must effectively "compete" for

one's death. The significance of an increased lifetime risk is that people may die earlier and possibly more unpleasantly because of exposure to the hazard. The lifetime risk of lung cancer is about 11 times greater for a smoker than for a nonsmoker (43). Another way to describe lifetime risks is to estimate the average loss in life expectancy due to the hazard. For the smoking example, one estimate of the loss is 8.6 years (6).

An *annual* risk is the probability of experiencing some adverse effect in the next year. Such risks will usually vary remarkably with a person's age, sex, and other factors not related directly to the hazard. Some risks are also changing with time. For example, the risk of stomach cancer from 100 rads of x-ray radiation could be declining because the baseline risk of stomach cancer is declining in the United States.



## *Individual and Population Risks*

The above examples seem to describe the probability that a person will experience an effect from a given hazard. Actually, of course, a specific person will either experience the effect or will not, and that person's own risk is either 0 or 1 over the defined period. But if we calculate the probability in a group of reasonably similar people, we can assign that probability as the *individual risk* for each member of the group.

If a group of $n$ similar people are all exposed equally to the same hazard with individual risk $p$ per year, then $pn$ is the total number of people that will experience the effect in that year. This number, $pn$, is the *population risk*. By adding up all the population risks over all exposed groups in the United States, we obtain the US population risk, $N$ (cases of the effect per year), or

$$N = \Sigma_i \, p_i n_i$$

where each $p_i n_i$ is the population risk disaggregated by exposure and susceptibility conditions. Thus if the population risk of death from lightning is 110 in 230 million people (23), individual risks can be higher or lower but average about one in two million.

## *Absolute and Relative Risks*

The above numbers are *absolute* risks in the sense that we estimate how many effects—in total or in excess over the baseline number *(baseline risk)*—are expected in a given population. The difference between the risk in an exposed population and that in a comparable unexposed population is the *excess risk*.

We can also estimate *relative* risks, the ratio of the absolute risk in the exposed population to that in an otherwise comparable unexposed population. The relative risk is easy to compute from an experiment, as it is just the ratio of the observed numbers of cases in the exposed and control groups, adjusted if necessary for the surviving number of individuals in each group. The rela-

tionships between the absolute risk *(AR)*, the baseline risk *(BR)*, the excess risk *(ER)*, and the relative risk *(RR)* are as follows:

$$AR = BR + ER \quad RR = AR/BR \quad RR = 1 + ER/BR.$$

Relative risks tend to be used to assess the degree of enhancement of risks by a hazard, whereas absolute risks are used to judge the overall magnitude of a problem. Whether a hazard with a small absolute risk but a large relative risk is more or less worrisome than one with a large absolute risk but a small relative risk is a difficult social choice.

### *Risk Assessment and Risk Management*

The National Research Council (35) has pointed out that value judgments and policy decisions are bound to enter any supposedly objective assessment of risk. But it also is clear that the process of risk assessment should be separated from that of risk management as much as possible. The NRC committee made the following distinction:

1. "*Risk assessment* is the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations."
2. "*Risk management* is the process of evaluating alternative regulatory options and selecting among them. A risk assessment may be one of the bases of risk management." (Emphasis added.)

Although most risk assessments have hidden nonobjective assumptions or values (54), this review does not further address risk management.

## TWO ESSENTIAL COMPONENTS OF QUANTITATIVE RISK ASSESSMENT

Two activities are essential for quantitative risk assessment: exposure assessment and effects assessment (39). Exposure assessment characterizes the degree and patterns of a population's exposure to a hazard, whereas effects assessment describes the response of the population to the exposures, in terms of probabilities and severity of effects. The two are combined to yield a quantitative population risk assessment.

### *Exposure Assessment*

Exposure assessment entails the estimation of the following:

1. Who is exposed? What are the characteristics (age, sex, race, etc.) of the exposed population? How many people of each type are exposed?
2. What is the source of exposure? Occupational activities, consumer products, environmental pollution?

3. What are the routes of exposure? Oral, dermal, respiratory, parenteral?
4. What are the magnitudes of exposure? Concentration in air, amount ingested per day, total radiation dose, hours exposed to sunlight?
5. What are the time patterns of exposure? All at once, protracted exposure, fractionated (divided) exposure, exposure increasing or decreasing with time?
6. What other exposures may influence risks? Are there known synergists?

Exposure assessment should be based on measurements when feasible; for example, the distribution of concentrations of a chemical in ambient air can be estimated by measuring concentrations in selected representative locations, or radiation doses can be estimated by providing nuclear power plant employees with personal dosimeters.

Often, however, the available measurements must be supplemented by a variety of theoretical and mathematical modeling techniques. A model for estimating the ingested dose of a pesticide may include an estimate of the amount of pesticide applied to farmland each year (source strength); the fraction of it that survives degradation by chemical and biological processes (persistence); how rapidly it runs off the land or leaches into groundwater and reaches streams (mobility); the dilution of the material by streamflow; the efficacy of removal in the water treatment plant; and the rate at which water from the public water supply is ingested.

Perhaps the most difficult challenge of exposure assessment is to estimate exposure in terms that permit integration of the exposure information with the requirements of the effects assessment. For example, if the dose-response relationship is expressed as a function of the dose to a particular organ, then in making the exposure assessment one will need to estimate or measure the pharmacokinetics that convert an ingested dose to an organ dose, perhaps taking into account metabolic activation or deactivation. To enable workable regulations, however, exposures must also be expressed as controllable measures such as parts per million in food.

Exposure assessment is a developing science, featuring ad hoc approaches developed for specific assessment needs. The need for more and better exposure estimates was highlighted in the recent report on *Toxicity Testing* (38), and several recent publications have compiled information on both general principles and specific applications of exposure assessment (5, 7, 50).

## *Effects Assessment*

Often, quantitative risk assessment entails only the estimation of the dose-response relationship for the hazard under study. For example, an agency might decide (as part of the risk management process) that a lifetime risk less than one in a million of dying of a certain effect was acceptable. Then the objective of the quantitative risk assessment would be to determine what exposure standard would limit the risk to one in a million. Prudent safety factors could also be

applied to the allowable exposure to account for uncertainties and variability of the population.

In any case, the effects assessment—also called hazard assessment (39)—is intended to estimate individual risks as a function of exposure variables and individual characteristics. The analyst attempts to estimate an annual or lifetime risk for incidence of the effect or mortality from it, conditioning the estimate on characteristics of the exposure and of the exposed person such as total dose, dose rate, route of exposure, age at exposure, duration of exposure, sex of exposed person, and health status.

As with exposure assessment, the effects assessment can be based wholely on measured information or on a combination of measured and modeled responses. If an exposed human population has been extensively studied, it may be possible to create a dose-response relationship that shows what fraction of the exposed group developed the effect at various exposures. If this relationship is applied to a similar group with a similar distribution of exposures, then the prediction of that group's risks should be reasonably informative and adequate for decisions on controlling exposure. Often, however, the exposures in the studied population are far higher than those of interest for the risk assessment, or the only information on risk comes from experiments on animals or cellular systems in the laboratory (46). In such cases, the analyst must extrapolate from animals to humans or from high doses to low ones, possibly taking into account other variables such as dose rate or age at exposure.



## MODELS: EXTRAPOLATION OF DATA

Several issues are subsumed in the general problem of extrapolating or projecting risks from one situation to another. By far the most familiar is the use of a dose-response relationship to predict the risks of low exposures from excess effects seen at greater exposures. Projecting to human risks from animal experiments, usually with rodents, is a second major concern. A third important task is to distribute observed excesses of effects over time after exposure, so that predictions can be made for times longer than the observation periods for human epidemiologic studies. Other issues include the influence of differing susceptibilities to the hazard and the differences in the biology of hazardous materials between species and between low and high doses (41). The examples used below are drawn from the literature on cancer risk assessment, but the issues apply in assessments of other types of effects as well.

### *Dose-response Relationships*

Statistically significant excesses of effects can be observed in experiments or observational studies of reasonable size only if the exposures to the population are sufficient to cause relative risks greater than about 1.5 (13). Such an excess

in a large population might be unacceptable, and we are often interested in increases measured in tenths of a percent. Thus dose-response relationships are used to extrapolate from the doses at which effects can be observed toward doses at which the excess approaches zero. (If any background exposure and any baseline or spontaneous rate of the effect are subtracted out, then the dose-response relationship must show no disease with no exposure.)

In chemical carcinogenesis, common models are the probit (24) and logit (11) models, which postulate distributions of susceptibility in the exposed population; the one-hit model (18), which supposes that the carcinogenic process is begun by a single event whose probability is directly proportional to dose; the multihit model (42), which supposes that two or more events, each depending linearly on dose, are necessary for cancer induction; and the multistage model (1, 9), which assumes that cancer development moves through several stages, each of which might be affected by the chemical.

In radiation carcinogenesis, the dose-response relationship is usually described as a polynomial in dose. The data are fitted to functions that are linear in dose, purely quadratic in dose, or contain both linear and quadratic terms (32). Theories of DNA strand breakage and chromosome rearrangements are hypothesized to explain the presence of linear and quadratic terms at low doses. Radiation risk assessments may include a term that declines with dose to account for cell-killing by radiation, which leaves fewer cells capable of expressing a radiation-induced carcinogenic transformation. Recently, conferences sponsored by the National Cancer Institute (25) and the Brookhaven National Laboratory (4) have attempted to unify the fields of chemical and radiation carcinogenesis.

The premier difficulty of quantitative risk assessment is that several dose-response relationships provide equally good (or equally bad) fits to the available experimental data in either experiments with laboratory animals or observations in human populations. Yet the response predicted at low doses frequently is exquisitely dependent on the dose-response relationship selected. For example, one assessment of saccharin risks (28) used data from experiments in which rodents were fed saccharin ranging from 0.005 to 5% or more of their diet. The human consumption for which the risk estimates were made was about 0.0001% of the diet. Even with a single method for projecting from rodents to humans (surface area), the predicted risks ranged from 0.001 to 1200 lifetime cases per million exposed, depending on the model used.

The critical problem is the shape of the dose-response relationship between the region of observations and zero dose. For radiation by alpha particles or neutrons, the dose-response relationship may be nearly linear over the low-dose region, declining in slope at higher doses (52). For radiation by X-rays or gamma rays, radiobiology suggests a quadratic behavior over much of the range, perhaps with a linear component becoming significant at very low doses (26). The slope of the dose-response curve may occasionally increase as it nears

the origin, perhaps because hypersensitive groups have steeper (linear) dose-response relationships than the general population, and only their experience would be observed at low doses.

A generalized dose-response curve is shown in Figure 1. Note that the response may appear linear or more or less than linear, depending on which part of the curve is emphasized. Whether a low-dose extrapolation underestimates response or overestimates it depends both on the true shape of the curve and on what part of the curve is represented by the available observed data.

## *Animal-to-Human Extrapolation*

To be timely in preventing the occurrence of disease, risk assessments are performed with essentially no human data from which to estimate the coefficients of the dose-response relationship. For example, the debate in the Environmental Protection Agency on whether or not to regulate formaldehyde as a carcinogen (49) stems in large part from the fact that the human epidemiology is not strong enough to support risk estimates, and quantitative risk assessment

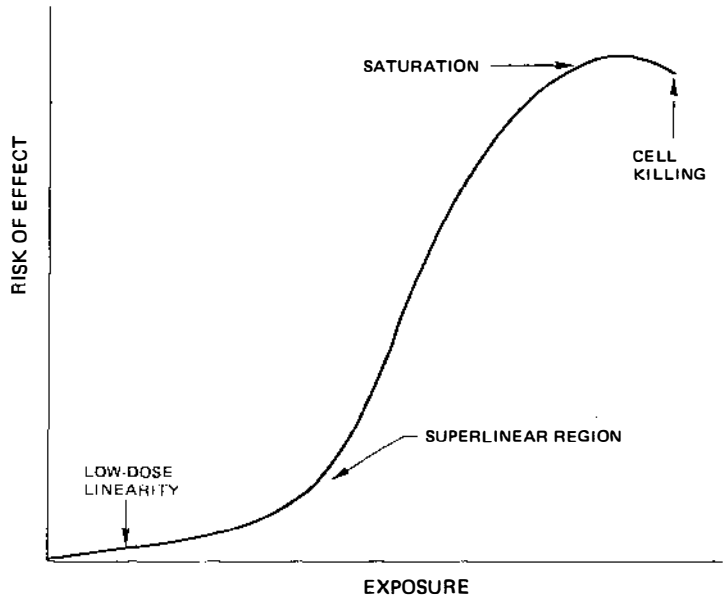


*Figure 1* Conceptual dose-response relationship, showing variation of risk with level of exposure, both in arbitrary units. For specific hazards, parts of the curve may be insignificant, leading to nearly linear responses in some cases, nearly threshold responses in others, and so on. Saturation may occur at less than 100% response. Over- or underestimates of responses at low exposure levels can occur when extrapolations are made from data at higher exposures; the direction and magnitude of the error depend on the detailed shape of the curve and the exposure levels at which the data were gathered.

must depend on animal experiments (47). Carcinogenicity in animals is usually assumed as sufficient to label a chemical a "presumptive human carcinogen," but both the sites of occurrence and the potency in animals correlate only loosely with those in humans for chemicals that are known to be carcinogenic in both (30).

The biology and biochemistry of animals can be vastly different from humans. For the formaldehyde example, rodents are obligatory nose-breathers and may show a different nasal cancer response than would humans. Moreover, rodents have much greater rates of metabolism, different routes of chemical processing, and much shorter lifespans.

To estimate what dose in humans would be equivalent to experimental doses in animals for the same annual or lifetime risk, at least four different projection rules have been used: direct use of concentrations, adjustment by body weight, adjustment by body weight and lifetime, and adjustment by surface area. The projected differences in human response to a given dose can be substantial. In the saccharin risk assessment (28), the projection rule made a difference of up to 200 times in lifetime risk. The comprehensive summary by the Office of Technology Assessment (40) shows differences up to 40 times.

## *Time-Response Models*

In many quantitative risk assessments, the analysis must stretch the data thin to estimate even the lifetime risk of an effect. In some situations, however, one may wish to predict the time course of risk after exposure to the hazard. The large, well-defined population exposed to radiation from the nuclear weapons detonated over Hiroshima and Nagasaki (53) makes it possible to study the time course of the appearance of certain cancers. In that population, incidence and mortality for various leukemias appeared to rise above the baseline about two years after the exposure, peak at seven to 20 years, and slowly decline toward baseline thereafter (15).

For radiation-induced breast cancer, the excess risk appears to be proportional to the baseline risk, rising with age and not observable until the age at which breast cancer rates begin to rise in unexposed women (20). Even in women old enough to develop breast cancer, the rise seems to be delayed for a minimal latent period of around ten years, although an excess probably could have occurred earlier without detection. This proportionality is consistent with relative risks being constant with time after exposure. One hypothesis is that radiation simply provides more initiated cells, which are then promoted over time in the same way as the cells that are involved in the baseline rate.

In other cases, the absolute excess risk may be constant with time after exposure. Such observations could be explained as the action of a complete carcinogen that initiates and promotes the cancers independently of any other initiating or promoting processes.

Time-response models effectively estimate the distribution of the latent period between exposure and the observation of effects (51). Even if an exposure immediately produced a viable cancer cell, a minimum time of a year or two might be required for it to multiply sufficiently for the solid tumor to be detected. Other factors may make this minimal latent period longer. Whether the length of such promotional stages is fixed for an individual person or varies by chance is not known. In some cases, exposure to the hazard may simply shorten the time course of cancer development (17). Mammary tumors are virtually universal in some strains of experimental animals, and carcinogens appear to advance the increase of the baseline incidence rate (Figure 2). With genetically diverse human populations, such a pattern may be difficult to demonstrate.



## *Variation of Susceptibility versus Stochastic Processes*

A stochastic process is one governed by the rules of chance. In cancer risk assessment, it is frequently assumed that the same exposure for similar people will produce cancer in some people and not in others and that which people develop the cancers is simply a matter of chance. For such stochastic effects, the dose-response relationship simply describes how the probability of the effect increases as dose rises, and its shape depends on the probabilities of various events leading to the effect.

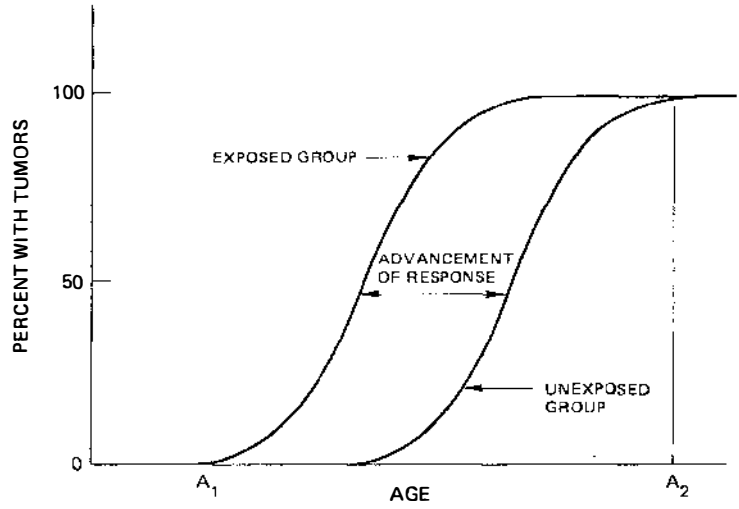


*Figure 2* Illustration of advancement in time of occurrence for tumors. Even an unexposed population is represented as having 100% lifetime risk. Thus the effect of exposure to a carcinogen may be interpreted as an advance in the time of occurrence. However, excess annual risk occurs at all ages between $A_1$ and $A_2$.

For other effects, such as carbon monoxide poisoning, some people are more susceptible to the effect than others, and the dose-response relationship simply shows the proportion of people who are affected by a given dose or lower. The shape of the dose-response curve then describes the distribution of susceptibilities in the population. Only in a highly homogeneous population could a clear threshold of effect be observed.

## *Thresholds and Pharmacokinetics*



Intoxication by carbon monoxide occurs because its molecules take up the sites in hemoglobin normally occupied by oxygen and depress oxygen transport. Even though carboxyhemoglobin forms at any concentration of carbon monoxide in inhaled air, essentially no clinically important effects occur unless the concentration rises to a point where the lowered oxygen transport capacity seriously depletes tissue oxygen. At higher exposures, the effects of oxygen starvation rapidly increase and death may result. The resulting dose-response relationship for mortality shows a range of concentrations where no deaths ever occur, followed by a steep rise representing individual susceptibilities related to oxygen capacity and needs, and a saturation region where everyone dies. The concentration at which the mortality probability begins to rise is the *threshold*.

Classical toxicology assumed that some accommodating mechanism would take care of low level insults for most toxicants; it followed that in setting allowable exposures, application of a prudent safety factor would prevent any occurrence of the effect. Next, the idea that some effects were stochastic implied that any exposure, however low, would have some probability of (say) initiating a cancerous lesion, that occasionally this lesion would escape all repair processes and be subjected to all promoting processes, and that a frank cancer would result. Radiation is generally conceded at present to have no threshold for carcinogenesis, even though the low-dose response may not be linear.

A counter-trend to this no-threshold idea has recently arisen. Cornfield (8) has argued that if chemical activation within the body is required, a minimum number of molecules must be taken in for any effect to occur. Although maintaining the possibility of a zero threshold, Hoel et al (14) have shown that nonlinear kinetics in the transport and conversion of chemicals in the body can lead to an effective threshold. They hypothesize that the carcinogenic effect depends on binding of a proximate carcinogen to DNA and that only in terms of the amount of bound DNA adduct will the dose-response relationship be linear. Repair of lesions as well as nonlinearities in excretion, metabolism, or potentiation of the initial chemical will make the response nonlinear in administered dose. Such a pharmacokinetic model may be able to explain why the responses of animals to high doses of vinyl chloride was less than one would expect from a

reverse extrapolation to the experimental animal from the experience in human populations (12).

## DEALING WITH UNCERTAINTY

Quantitative risk assessment is handicapped by great uncertainty in its estimates; its use could be quite inappropriate if these uncertainties are not recognized by the decision makers and the affected public (31). Risk management is much more likely to be evenhanded and prudent if the uncertainties in risk assessment are understood, and neither dismissed or exaggerated.



### *Uncertainties in Data, Assumptions, and Models*

Uncertainties in data are easy to understand. We measure the concentration of a pollutant in indoor air three times and the results are all slightly different. Both problems of measurement and the inherent variability of the concentration of the pollutant may be involved. We count the number of tumors in experimental animals and compute the risk at a given dose. There may be errors in deciding what to call a malignant tumor, uncertainty whether the control group was really the same as the test group except for the dose, and always the inherent variability that will yield different numbers if the experiment were replicated. Epidemiology may show two excess genetic abnormalities in a large exposed population; one is unsure even whether an association exists, and certainly discounts any risk estimate derived from those two cases.

But such uncertainties are often only the least of our worries. What have we assumed about the similarity of people to experimental animals? About the relative effectiveness of exposure by different routes? About the susceptibility of infants if the epidemiology was done with adult populations? Often the uncertainties due to assumptions are not even identifiable, because the assumptions were never made explicit, even in the mind of the investigator. Even with explicit assumptions, we rarely have a satisfying way of estimating the degree of uncertainty.

Finally, we must almost always extrapolate from situations in which risks can be observed to ones in which they are only suspected. Not only do we have the problem of which extrapolation model to choose, but the parameters of any one model are based on a statistical fit to observed data which are themselves uncertain and variable.

### *Ways of Expressing Uncertainty*

Qualitative expressions of uncertainty have their place, especially if certain data or conclusions derived from them seem so flawed as to be useless. In general, however, more quantitative expressions of uncertainty are needed to judge better how much weight in decision making to put on the various components of the risk estimates.

For data uncertainties, statistical confidence limits or sometimes a complete distribution of probabilities can be generated. For other types of uncertainties, it is sometimes possible to establish the range of plausible values for an estimate, defining the lowest and highest reasonable values. Unfortunately, ranges can often be mistaken for confidence limits and vice versa. The analyst needs to be clear about what the numbers mean.

For uncertainties in assumptions and models, the only realistic resort may be to use the subjective assessments of experts. Techniques of decision theory permit one to combine the uncertainties in exposure assessment (say) with those in dose-response relationships to derive overall uncertainties in population risk estimates.



## TWO EXAMPLES

### *Predictive Risk Assessment: Ambient Asbestos*

The Environmental Protection Agency requested the National Academy of Sciences to form a committee of the National Research Council to examine the health risks of nonoccupational exposure to asbestiform fibers (29). Among other tasks, the committee decided to undertake a quantitative risk assessment of exposure to asbestos in ambient air.

Although it is possible (and perhaps likely) that different types and sizes of asbestos fibers pose different risks, the committee decided to assess the risks on the assumption that fibers in the ambient environment acted like fibers in the workplace except for differences in concentration by weight. That is, if 1 fiber per $cm^3$ (optical microscopy) corresponds to 30 micrograms per $m^3$ in the workplace, then 30 nanograms per $m^3$ in the ambient air would act like 0.001 fibers per $cm^3$ in the workplace. Consistent with the available data from human populations, the response is also assumed to be linearly related to dose—other factors the same. Moreover, the committee assumed that, at least in the ambient environment where fibers are both shorter and finer than in the workplace, chrysotile (the asbestos variety most commonly used in the United States) was equal in carcinogenic potential per unit dose to crocidolite or any other amphibole asbestos.

Thus the committee had two tasks: (*a*) to estimate typical concentrations of asbestos fibers in ambient air, including both indoor and outdoor air, and (*b*) to estimate dose-response relationships for various potential health effects. The committee assessed only the risks of lung cancer and mesothelioma, assuming that few if any cases of asbestosis would arise from low concentrations in ambient air. Only human data from occupational epidemiology were used in the dose-response analysis.

For lung cancer, the committee adopted a relative risk model in which the exposure to asbestos multiplied the baseline risk by a factor depending only on total exposure to asbestos—expressed as the product of the concentration and

the duration of exposure. The coefficient of the linear relationship was taken as a median value from nine epidemiologic studies. For mesothelioma, the committee used a time-response model that, for a constant asbestos concentration in air, increased as a power of the time since first exposure. The committee chose 3.2 as the exponent, based on an empirical analysis of the data from five studies. Note that this model could become a relative risk model with a linear dose-response relationship if the baseline mesothelioma risk rose with the 2.2 power of time.

The committee examined several compilations of ambient asbestos measurements. In outdoor air, 0.00007 fibers per $cm^3$ may be typical; 0.0006 may be typical in indoor air. Weighting these estimates by the proportions of time spent indoors and out, the committee chose 0.0004 fibers per $cm^3$ to represent year-round average exposure for a typical person. For a highly exposed person who may live in an environment with high outdoor concentrations or spend much time in rooms with asbestos insulation, 0.002 fibers per $cm^3$ was chosen as a typical exposure.

The quantitative risk assessment predicts that 64 lifetime cases of lung cancer would occur in a million male smokers exposed at 0.0004 $cm^3$, 23 cases in female smokers, 6 cases in male nonsmokers, and 3 in female nonsmokers. The differences are due to the different baseline risks between men and women and between smokers and nonsmokers; they reflect a "multiplicative" effect between smoking and asbestos exposure as risk factors. For mesothelioma, 9 lifetime cases per million were estimated, independent of sex and smoking status. The risk is higher than for lung cancer for nonsmokers but lower for smokers. All estimates are computed for lifelong constant exposures.

Based on uncertainties in the statistical analysis of the available epidemiologic data, the committee estimated the upper bound of the risks to be 290 lifetime lung cancers per million male smokers and 350 lifetime mesotheliomas per million people. The lower limits of risk for both diseases were described as zero excess because it is not clear whether low level exposures to small fibers are equivalent to high level exposures to much longer fibers, even if adjusted for dose. Both differences in biological response to fibers and the possibility of a threshold in the dose-response relationship may be involved.

## *Retrospective Risk Assessment: Cancer and Radiation*

Quantitative risk assessment can also be employed when the problem is retrospective: What is the likelihood that a person's cancer is related to a previous exposure to a hazard? For many cancers, e.g. lung cancer, the possibly causative agents are multiple: smoking, radiation, arsenic, and so on. Some lung cancer may also occur spontaneously through random imperfections in natural biological processes. Therefore, when a cancer develops after exposure to some potentially causative agent, it is not certain that there is a causal connection. Sometimes the connection is nearly certain because of the unusual

nature of the cancer (mesothelioma or angiosarcoma), and sometimes it is reasonably probable because of the detailed nature of the tumor tissue (squamous cell versus basal cell carcinoma of the skin, for example).

But for some agents, such as ionizing radiation, the cancers produced are indistinguishable from ones related to other causes or ones that occur spontaneously. How then does one evaluate a claim for compensation? If the cancer is otherwise rare or the dose is high, the relationship may be easy to establish. When the dose is low and the cancer common, however, the causal connection, while possible, may be improbable.

Bond has suggested (3) a probabilistic attribution of cause for potentially radiogenic cancers. The Orphan Drug Act of 1983 (PL 97-414) contained in its section 7(b) a directive that the Secretary of Health and Human Services "devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses."

Such "probabilities of causation" have been estimated for a limited set of cancer sites, ages at exposure and at diagnosis, doses delivered, sex of exposed person, and other factors (27). Such tables, however, are beset with a host of difficulties, not least of which is that few, if any, cancers have only one cause (36). The probabilities can only be estimated in the context of a comparison between an exposed and an otherwise equivalent unexposed population; thus the term "probability of causation" is possibly misleading by suggesting mutually exclusive causes with probabilities calculable for an individual person.

Other major difficulties in estimating probability of causation relate to the choice of the form of the dose-response relationship, the time-response model, the latent period assumptions, and the partition of the population to be used in producing the tables. (A partition determines, for example, whether separate tables are produced for smokers and nonsmokers or for whites and nonwhites.) Uncertainties in the computed probabilities will be substantial because of these difficulties. Whether the tables will permit an improved basis for compensation depends on the circumstances of the situations to which they are applied and the compensation rules that are tied to them.

The idea, however, is appealing from a risk assessor's viewpoint, because it acknowledges the idea of stochastic risks and legitimizes the quantitative risk assessment process. The concept is certainly not limited to radiation, and could in principle be applied to a variety of chemical and physical risk factors, and to end points other than cancer. However, there are few examples of stochastic risks understood better than the relation of ionizing radiation to cancer. We shall have to appraise the success of the idea in that limited field before exploring its utility for other problems of retrospective risk assessment.

## SUMMARY AND CONCLUSIONS

Quantitative risk assessment may never become a rigorous scientific discipline because of the inherent difficulties in working with highly uncertain and often controversial data and methods, and because the predictions of risk assessment may not be subject to validation in their most important areas of application. However, the potential benefits of having quantitative estimates of risk may make quantitative risk assessment a valuable adjunct to traditional methods for making individual and social decisions about health hazards in the home, workplace, and general environment.

Risk assessment, which is the process of estimating risks to populations exposed to hazardous agents or activities, must be distinguished from risk management, which is the process of forming and implementing a strategy for accepting or abating the risks. To the extent possible, these two processes should be kept separate.

Quantitative risk assessment is in principle capable of estimating individual or lifetime excesses of specific health effects from exposures to a specified hazard. These excesses may be estimated on an absolute basis or expressed as a relative risk in comparison with the baseline risk that would exist without exposure. An individual risk is usually expressed in terms of the probability of developing the health effect in some time period following a specified exposure, whereas a population risk is the overall number of effects expected in a defined population with a defined distribution of exposure levels and patterns. The variation of risk with time after exposure may imply a constant absolute risk, a constant relative risk, or some other dependence on time, usually after a minimal latent period has elapsed.

Risk estimates can rarely be made directly from observed human data, and models for extrapolating or projecting risk estimates from the conditions of observation to the actual conditions of exposure must be used. Dose-response relationships are used for extrapolating from high laboratory or occupational exposures to low exposures encountered more frequently in human populations. Thresholds of dose or nonlinear dose-response relationships may be related to nonlinear pharmacokinetics prior to the ultimate exposure of the critical organ to the proximate carcinogen or other hazardous agent. Time-response models estimate risks for periods after exposure longer than have been observed in epidemiologic studies. Extrapolations from experiments with laboratory animals to humans are made difficult because of great differences in size, lifespan, physiology, and metabolism between human and animal.

Uncertainty is commonplace in quantitative risk assessment and must be discussed explicitly to avoid the undue impression of reliability that is often suggested by quantitative estimates. Uncertainty comes from measurement problems, inherent variability, unverified assumptions, and imprecise projec-

tion models. The substantial resulting uncertainties in the risk estimates can be described qualitatively or quantitatively through confidence limits, ranges, or subjective uncertainty distributions. A true accounting of the uncertainties may make difficulties for decision makers that might have been concealed in a qualitative risk assessment process.

With all its drawbacks, quantitative risk assessment is being found more and more useful and increasingly more acceptable as one of the bases of decision making about hazards to public health. At the least, it forces the decision makers to be more systematic and explicit about the assumptions they make and the uncertainties they face.



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