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Thresholds for Carcinogens: A Review of the Relevant Science and Its Implications for Regulatory Policy

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Abstract

Regulation of carcinogens in the United States has been based on a "no threshold" policy. This makes the assumption there exists no level of exposure for which the possibility of causing harm is truly zero. The alternative "threshold" policy assumes that there exists some level of exposure at which no harm will come to anyone in a population so exposed. The no-threshold policy made sense when adopted, thirty or more years ago, since the science then available was not able to distinguish between these two opposing hypotheses, and "no threshold" provides more margin of safety. Since then, our understanding of biological processes related to birth and growth of cancer has greatly expanded. We now understand that two different biological processes can enlarge cancer risk. Increasing the rate at which cells divide is one of these; increasing the rate at which mutations occur, independently of cell division (mitotic) rate, is another.

It is known that mitotic rate is under close physiologic control, operated through a complex system including a variety of intercellular messenger molecules. Functions controlled so as to be kept within certain limits in the face of external stressors must by definition exhibit a threshold in their response to small changes in such external stress. It is only necessary to demonstrate the existence of physiologic control to show that the threshold must exist. Thus there will be a threshold in the response to any nonmutagenic ("*mito*genic") carcinogens.

For classical mutagenesis as well, the weight of evidence favors the conclusion that thresholds exist. Evidence for "no threshold" has almost no weight, either because of the limits on our ability to measure response at very low levels of mutagenic stimulus, or because it springs from an unacknowledged tautology. Conversely, there is evidence of moderate weight, primarily that cancer rates are not elevated in areas of high background radiation flux, that the mutation rate is under active physiologic control.

This expanded knowledge allows more reliable guidance for policy makers. First, policy should distinguish between "mitogenic" and "mutagenic" carcinogens, those that act predominantly by increasing the rate at which cells in certain tissues divide, and those that act directly on DNA. Mitogenic carcinogens should receive the same treatment as "noncarcinogens." At EPA, at least, policies are changing to reflect this understanding. Mutagenic carcinogens should be regulated using the "*de minimus*" approach FDA and EPA use for all cases other than direct food additives and pesticide residues. This approach relies on the concept of a "practical threshold," and provides very adequate protection of public health.

Key Words: regulation, cancer, science policy

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Thresholds for Carcinogens: A Review of the Relevant Science and Its Implications for Regulatory Policy

James D. Wilson[1]

INTRODUCTION

This paper is intended to examine the scientific basis for choosing between two opposing theories about the process by which cancers start, and the public policy implications of that choice. For policy purposes, it is important to understand this process and how it is affected by human activities, particularly by the new chemical substances whose use has transformed modern civilization. People come into contact with and absorb these substances, frequently at levels that are very small compared to amounts that cause discernible harm. The tools available to science only very rarely permit a direct determination of the likelihood that injury will occur from such very small levels of exposure. Thus policy makers must rely on scientists' judgment of that likelihood, a judgment that is heavily influenced by prevailing theories of cancer and carcinogenesis. Over the past twenty-five years the consensus on these has evolved, and with that evolution comes a change in recommendations for policy.

The two opposing theories concern the behavior of cancer "dose-response" relationships. These relationships are expressed in terms of mathematical functions that describe how cancer incidence ("response") changes with levels of exposure ("dose") to

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carcinogens. In technical terms, the proposition we wish to examine concerns the behavior of these functions as exposure becomes "arbitrarily small" -- but not zero.[2] One of these, the "threshold" theory, holds that increased incidence (over background) becomes zero at some nonzero exposure. The other, "no threshold," holds that increased incidence becomes zero only at zero exposure. Until very recently public policy has officially been based on the "no threshold" theory.

Until the 1950s it was a well-established tenet of toxicology that for any poison there exists a threshold dose below which exposure poses no risk. Late in that decade, regulatory scientists proclaimed that for carcinogens, "no safe dose exists" [Fleming, 1959; Mider, 1960]. This proclamation occurred near the beginning of three decades' worth of laws and regulations intended to protect human health and our environment. Now we are engaged in a great reconsideration of the policy edifice built in those decades, asking whether those laws and regulations should endure. As part of this reconsideration it is appropriate to examine the scientific basis for the laws and regulations, to ascertain which parts are well founded and which stand on sand.

The "no threshold" policy has always been controversial. Biologists almost universally believe that thresholds always exist. Mathematicians point out, correctly, that the curves biologists use to represent reality, for relationships such as that between exposure and response, are uniformly continuous, infinite, monotonically increasing functions that do not

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[2] "Arbitrarily small" means that we are allowed to choose a level of exposure that is as small as we wish, approaching very near to zero but not reaching that absolute value. In this case, we are interested in exposure values that are less than what can be measured experimentally, but not in any specific exposure value.

admit a discontinuity such as a threshold. Further, the uncertainties in ascertainment of exposure and response are large enough to prevent any direct experimental test: the "noise" is large compared to the "signal" one hopes to detect. At the time the "no threshold" policy was established, scientific theory could provide little guidance to policy makers. The "threshold" and "no threshold" options were equally plausible. Thus, sensibly, regulatory scientists urged adoption of the more protective policy, that based on the "no threshold" theory [Mider, 1960; OSHA, 1980].

Over the last twenty years the situation has changed. We now understand much better both how cancers start and grow and how biological functions are regulated. There is now a consensus that thresholds exist for some kinds of carcinogenic processes [EPA, 1996]. We suggest here that the weight of evidence favors the view that thresholds exist for all such processes. Policies should be adjusted accordingly. Doing so need make no change in the degree of health protection.

This Discussion Paper is intended as a contribution to science policy. Thus the argument flows from a review of the current situation -- recapitulating the meaning of "threshold" and policies that depend on its interpretation -- followed by a summary of the new science relevant to these policies and then some conclusions about policies. The discussion is based on a theory of how science contributes to policy formation, provided as an Appendix to this paper.

Situations such as the "threshold" debate provide a rigorous test of science. Whether or not a threshold exists cannot be answered by direct test. It is beyond reach of the kind of experiment or study that provides scientists with the strongest support for their beliefs. We cannot *know* how the dose-response curve actually behaves as it approaches arbitrarily close to

zero effect. ("To know" something should be understood to mean "to have great confidence in" some conclusion.) Because the conclusion is intended to inform public policy in which individual scientists may well have a stake, it becomes very important that all the evidence be reviewed, discussed, and weighed as fairly as can be done. It is equally important that any conclusion be accompanied by a frank discussion of the uncertainties: if the uncertainty is large and the confidence not high, public policy may best be served by a choice that does not reflect the current scientific consensus.

THE MEANING OF "THRESHOLD" AND CURRENT APPLICATION TO POLICY

Like many useful concepts, "threshold" carries somewhat different meanings to different specialties within science and the public health profession. To pharmacologists (with whom it appears to have originated) the idea is straightforward: there are always doses (levels of treatment) that are without discernible effect on those being given drugs. In this application, the theory of a threshold for activity is not controversial. It is, in fact, universally accepted and applied. Centuries of observation support the idea.

It is useful to refer to the pharmacologists' concept as a "practical threshold."[3] It implies that responses which cannot be observed have no practical significance. Theory may admit the possibility of some response at low exposure, or predict an undetectably small one yet for practical purposes these may be neglected. Much of our current policy edifice for dealing with carcinogens actually stands on this concept. It is, for instance, consistent with the

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[3] The terms "effective threshold" and "threshold of regulation" are used to refer to essentially the same concept.

"no significant risk" standards common in environmental statutes [Byrd and Lave, 1987; Barnard, 1990; Cross *et al.*, 1991].

To people dealing with public health policy, "threshold" carries a more stringent implication: at some nonzero exposure the response not only passes below the limit of detection, and not only approaches zero as a limit, but becomes exactly, identically zero.[4] Biologists appear to believe that the thresholds they observe are absolute, but the question has not been one of much interest; and for them the "practical threshold" concept suffices.

There have been circumstances where, for public health officials, the practical threshold has not sufficed. These officials are charged to provide the public with credible advice regarding safety. Their credibility depends on their confidence that they understand the hazards facing the public. They can confidently declare exposures safe when no adverse effect can be identified, if a threshold exists. However, if they believe no threshold exists, their confidence may be much less. The practical threshold states only that no harm can be detected; such a prediction may well not be acceptable, because the ability to detect such harm is not very sensitive. Detectability is set by the year-to-year variability in cancer death rates[5]; for most this is at least 2-3% of the annual rate. For the more common cancers, these annual rates fall in the range of tens to thousands to hundreds of thousands of deaths per year. Thus

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[4] We will leave aside the issues posed by essential nutrients such as selenium, and the complications introduced into analysis of dose-response curves by competing causes of mortality. It can be taken as given for policy purposes that for truly essential nutrients, a threshold has to be assumed. There has been considerable discussion, not yet resolved, of this issue in the instance of a drinking-water standard for arsenic.

[5] Because most cancers result in death, public health professionals have generally used the death rate as a measure of or surrogate for the harm cancer causes.

exposure to some specific chemical might cause thousands of deaths without detection.[6] Half a century ago, as we began to give serious consideration to protecting against radiation and chemicals that cause cancer, it was regarded as not acceptable to the public that such a situation might be regarded as "safe." At that time theory suggested that there might not be a threshold for exposure to substances that may cause this dread disease. So the profession recommended basing policy on the assumption that no threshold exists. From this came the phrase, "There is no safe exposure to a carcinogen" [Mider, 1960].[7]

The "no safe exposure" dogma reflects the paradigm of carcinogenesis that was current through the 1960s. This theory implied that all cancer occurs as a consequence of the reaction of "carcinogens" with DNA. [Olin *et al.*, 1995]. The typical carcinogens then recognized react with DNA in much the same way as related low-molecular-weight model compounds react. Almost all such carcinogens come from the chemical family of "electrophiles." DNA-like molecules react with these in a way that gives rise to a direct proportionality between dose and effect. Given this theory, a no-threshold, linear relation between very small chemical exposure and cancer risk is quite reasonable.

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[6] For example, for adult men in the United States, the death rate from bladder cancer varies randomly between 55 and 65 per hundred thousand per year. With close to 100 million adult men in the U.S. population, between 55,000 and 65,000 deaths occur every year from this cause. Year-to-year increases (and decreases) of two or even three thousand deaths (5% of the mean rate) occur frequently. It is not possible to identify a change of this magnitude that may be due to some particular cause, in the face of random fluctuations of similar magnitude, unless it were to continue for many years. Note, however, that for rare cancers such as that caused by exposure to vinyl chloride, the detection limit is only a few deaths per year.

[7] Also contributing to this slogan was a lack of confidence among professionals in what should be considered "safe". They worried about absolutes. Lowrance [1976] has since shown that "safe" is not an absolute, but relates to a notion of acceptable risk. In the 1960s the public health profession was not certain that any degree of cancer risk would be acceptable. Today we have a better understanding of people's tolerance for different kinds of risks, in different situations. (For instance, we know that more risk is tolerated when those at risk feel able to exert some control over their own fates.)

The idea that any exposure to a carcinogen produces some risk to those exposed became widely established in policies of regulatory agencies in the United States between the late 1950s and the mid 1970s. Its first and most enduring formal expression was in the famous "Delaney Clause" enacted as part of the 1958 amendments to the Food, Drug, and Cosmetic Act (FDCA). This clause prohibits approval and thus use of intentional ("direct") food additives that "induce cancer". Although symbolically this language has great weight, in practice it has seen almost no use by FDA [Prival and Scheuplein, 1990].[8] The Food and Drug Administration already had the duty to keep all harmful substances from food. It can and has used its general authority from FDCA to ban carcinogens from the food supply.

FDA is also charged to assure that the food supply is adequate to our needs. This responsibility sometimes conflicts with the requirement that food be safe; FDA commonly balances these contradictory objectives by recognizing the ancient dictum "the dose makes the poison," *i.e.*, that sufficiently small amounts of the most deadly poison will do no harm. That is, FDA trades off certainty of safety for certainty of sufficiency to reach the needed balance. Under the general provisions of FDCA, FDA also can recognize the limitations of inferences for human response from experiments in animals, weighing the utility of such data in the regulatory balance. But with Delaney, Congress instructed FDA to adopt a different policy, assuming rigorously that safety could not be achieved with any amount of carcinogenic substance in food and taking at face value any results from animal experiments.

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[8] However, it may now force EPA to cancel certain pesticide registrations. See below, pp. 34-35.

Beyond extending Delaney to food colors and animal drugs during the 1960s, Congress has not written the "no threshold" idea into any of the many other health and safety laws.[9] Nevertheless, it has pervaded regulatory approaches to carcinogens, and extension to developmental toxicity has been proposed [Rai and Van Ryzin, 1985].[10] Notable examples of its impact include EPA's adoption of the "linearized multistage" procedure for evaluating cancer risks,[11] and the "Risk-specific Dose" hazard indices used for environmental regulations, the distinction that that agency makes between "carcinogens" and "noncarcinogens" in drinking water standards, and so on. It underlay the OSHA "Cancer Policy" proposed in 1977 (which has been neither withdrawn nor implemented) [OSHA, 1980], and continues to influence both OSHA's and FDA's regulatory approaches to substances called "carcinogens". It also is seen frequently in state laws and regulations, particularly California's "Proposition 65."[12]

Over the years, FDA has whittled down the applicability of Delaney, especially for "indirect" food additives [Merrill, 1988]. For these and for "contaminants" FDA's charge to maintain an abundant and healthful food supply has led it to adopt a *de minimus* policy [Prival and Scheuplein, 1990]. Most foods are now known to contain insignificantly small amounts of

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9 The authority to ban production of non-food substances was given to EPA in the Toxic Substances Control Act and to the Consumer Product Safety Commission. However these differ in being risk-based and not "no risk" [Lave, 1981].

10 Note that no regulations based on a "no threshold" assumption for endpoints other than cancer have been implemented.

11 This procedure assumes that the response is zero only at zero exposure, and calculates an "upper bound" on that response equal to the steepest straight line that can be said to be statistically consistent with observed dose-response in animals. It is used to set "no significant risk" standards, and sometimes misused to estimate responses [Wilson, 1991].

12 The Proposition itself is based on a "no significant risk" standard, recognizing the practical threshold. However, the California EPA implements it by means of "safe harbor" guidance developed using the linearized-no threshold dose-response methods.

naturally-occurring carcinogens [NRC, 1996]; banning all carcinogen-containing foods would mean we would have nothing to eat! Thus FDA has moved to the "practical threshold" to regulate carcinogens whenever it can. EPA once proposed to do likewise for pesticide residues [EPA, 1988]; that policy was struck down by the courts, and the Agency and affected and interested parties are trying to work out an alternative.

SCIENTIFIC CASE FOR A "NO THRESHOLD" ASSUMPTION

Three lines of argument have been used to support the "no threshold" policy. First, many sets of observations fit a nonthreshold mathematical model. Second, a theory that exposure to carcinogens adds to background processes implies that added exposure increases risk linearly. Third, if the underlying physical processes are either stochastic or otherwise are describable by statistical methods, mathematics requires that any nonzero exposure implies a nonzero added risk. These have some validity, and need weighing in a science-based conclusion.

Evidence from Curve-fitting

The first justification for assuming no threshold for carcinogenicity exists came from an observation on the effect of radiation treatment on single cells. The dose-response was fit by a straight line that passed through the origin. Subsequently, the theory of mutation-caused cancer supplied a theoretical basis for analyzing dose-response in this way. Still later, a second argument, based on treatment adding a small increment to an ongoing process, was raised [Crump *et al.*, 1976], to justify the assumption. Yet these arguments at best permit the interpretation that no threshold exists; they permit equally well the contrary argument.

Categorically, the fact that a curve with zero intercept "fits" a particular data set does not imply that a curve with nonzero intercept will not also yield an acceptable fit, especially to the kinds of data sets available in this field. Uncertainties are very large, compared to the intercepts expected on biological grounds. The original curve-fitting was done with pencil and graph paper. To anyone who has done such manipulation, it is obvious that such a procedure can equally well produce a line that supports a "threshold" interpretation. Such data that can be fit to a line of the form, $y = mx$ will also fit $y = mx + b$, with $b \neq 0$.[13] These data are simply too uncertain to allow distinguishing between "threshold" and "no threshold" hypotheses. [*Cf.*, for example, Figures 1 and 2 in Land, 1995 and Kitchin and Brown, 1994.] At best, the data permit setting a bound on the magnitude of a threshold.

Observations of dose-response from radiation-induced cancer do fit reasonably well to non-threshold curves[NRC, 1990]. Yet recent re-evaluations of some of the best of these data sets, including Hiroshima/Nagasaki [Delpla, 1988; Shimizu *et al.*, 1993; Alvarez and Seiler, 1996] and the "radium dial painters" [Thomas, 1995], using methods that allow the intercept to vary, have found better-quality fits are obtained with nonzero intercepts.

Additivity to Background

Crump and co-workers proposed that because background processes lead to cancer, exposures to carcinogens should be considered to supplement these processes, giving non-threshold, linear exposure-response functions [Crump *et al.*, 1976; Krewski *et al.*, 1995]. A

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[13] In fact, if b is permitted to vary the uncertainty in the data sets available is such that computer-generated fits to this data will usually return $b \neq 0$, just by chance, even if the true value of b were zero.

similar argument has been made by Crawford and Wilson [1995] for common adverse effects other than cancer, and in fact their case is stronger than that possible to be made for cancer. These arguments assume that dose-response curves increase uniformly from a zero response. "Additivity to background," as this is called, does imply a linear dependence of response on exposure. However, if the fundamental assumption that response begins at any added extra exposure is not correct, the straight lines will not pass through the origin. If no response occurs at some exposure, *i.e.*,a threshold exists for the effect, the intercept will be nonzero.

Stochastic Processes

Many of the biochemical processes involved in the chain of events between exposure to a carcinogen and the start of a cancer are of a sort usually described by the techniques of statistical mechanics. Using these techniques one can calculate quantities such as the fraction of molecules from a particular dose of reactive carcinogen that will reach cellular nuclei. These techniques were originally developed to understand nonequilibrium properties of gases; the typical problem involved estimating the probability that a fast-moving elastic ball bouncing around inside a box would pass through a small hole into an adjacent box in some period of time. This probability was found to depend on the speed with which the ball is moving and the size of the hole: the faster the speed (the higher its energy) and the larger the hole, the more likely it is that the ball will pass through into the next box. With an assembly of such balls and knowledge of the distributions of their energies, one can calculate such things as the numbers of balls found in the adjacent box during successive periods, and thus understand the rate at which equilibrium is attained and suchlike. In effect, the size of the hole can be equated to a barrier which the ball must surmount in order to pass from one "state" to another.

Entry of toxicants into the system (inhalation, ingestion, absorption, *etc.*) is describable by statistical mechanics; the rate depends on such measurable parameters as adsorption coefficient, partition coefficients between blood and air, *etc*. Once into the blood, molecules are transported everywhere, some to be altered by chemical reactions; all of this is describable by statistical-mechanical methods. At the molecular level, the reaction of a mutagen and DNA leading to a carcinogenic transformation is best thought of as one in which the attacking mutagen is hindered by a series of barriers that are not infinitely high, not infinitely efficient at disarming this invader.

Chemists and engineers commonly use statistical methods to analyze this kind of process. These very successful methods make a fundamental assumption that the probability of overcoming all the barriers is random, or "stochastic" and thus may become very small but never identically zero.

There are several of these barriers. One is metabolic transformation to an inactive substance, which includes reaction with protective elements such as the mucus of the respiratory tract and chemicals such as glutathione.[14] A second line of defense is DNA repair. Since DNA is constantly being damaged by various natural processes (mostly through oxidation), we have evolved very efficient enzymes that monitor the status of our DNA and repair it as necessary.[15] Work by Ames and his collaborators suggests an impressively high

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[14] It was puzzling, at first, that the chemicals that react most avidly with DNA components have relatively little carcinogenic or mutagenic potency *in vivo*. This was rationalized by noting that these chemicals are so indiscriminately reactive that at small doses they react with something else before reaching the cell nucleus, and at high doses they kill.

[15] Recently several genetic defects in DNA repair enzymes have been observed to be associated with an increased risk of cancer.

rate of repair going on constantly: they find excreted in urine oxidative degradation products of DNA bases that imply repair of *ca*. 10^4 defects per cell per day [Ames and Saul, 1986].

A third "barrier" arises from the relatively small number of effective target sites for a mutagen, compared to the total sites available. To give rise to a cancerous cell, mutagens must attack one of the few (~10^3/~10^7) genes that code for proteins involved in regulation of cell division and differentiation [Bradshaw and Prentis, 1987; Knudson, 1985] or in DNA repair, and do so in a cell that is capable of division. (Terminally differentiated cells, for example, don't reproduce, so any mutations that may occur in them are not passed along to other cells.)

Viewed in conventional terms, and demonstrably true with treatments that produce observable effects, each of these processes is stochastic. One can readily estimate the probability that a molecule of a mutagen will get past each of these barriers and cause an effective mutation in a critical gene. At exposures leading to observable effects, these estimates account for the effects observed.

The probability that any one molecule will effect a cancerous transition in a cell capable of starting a cancer is vanishingly small, 10^{-18} or less. Yet even this unimaginably small number is overwhelmed by the numbers of molecules that take part in an exposure capable of causing cancer. Because we can carry out experiments in mice, we know these numbers more precisely for these animals. Typically, for a moderately active mutagenic carcinogen in a mouse, cancers will be caused by single doses of ~50 mg/kg body mass. This corresponds to the order of 10^{19} molecules per mouse, or about 10^{10} per cell. Doses of this size usually result in a one or a few tumors, the results of attacks on DNA from the ~10^6 cells capable of

developing into a cancer that exist at any one time. Thus the "yield" of tumors per molecule of carcinogen is the order of 10^{-19}.

Because "effect" doses appear to scale with body mass, we infer that similar numbers of active molecules per cell are necessary for a single dose to cause cancer in humans. When the numbers of molecules are this large, stochastic models describe the process very well. We can readily account for differences in potencies among mutagenic substances by differences in metabolism, *etc.*, that make them more or less capable of overcoming these barriers.

However, for most "environmental" issues policy makers are concerned about rather different conditions, with exposures measured not in tens of milligrams per kilogram, but micrograms or nanograms or femtograms, not billions of molecules per cell but thousands or even less than one. For strong mutagenic carcinogens, the likelihood that a dose constituting some number of molecules will cause a cancer is less than the fraction it represents of the number known to cause cancer. From this it follows that at exposures totaling, say, a millionth of the number required for observation of tumors in a single-dose experiment, the likelihood of a cancer becomes vanishingly small. So if 50 mg / kg of a carcinogen causes tumors in any mouse examined, total exposures less than 50 nanograms / kg[16] will cause tumors in (many) fewer than one mouse in a million. This line of reasoning supplies very strong support for the "practical threshold" policies described above. If the likelihood of an exposure causing a cancer can be said to be negligibly small, the exposure can be considered safe [Lowrance,

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[16] A "nanogram" equals one one-millionth of a milligram. For a typically potent mutagenic carcinogen, such as benzo[a]pyrene, 50 nanograms / kg in a mouse works out to about 2500 molecules per cell, compared to the 2.5 billion per cell employed in single-dose experiments.

1976].[17] At such small exposures, no effects can or will be observed. (In fact, as we note below, the likelihood of cancer will be much smaller than this upper bound, because these carcinogens act as mitogens as well as mutagens, and their "potency" is much less than proportional to dose, with decreasing dose.)

This straightforward reasoning underlies the initial application of "quantitative risk assessment" to a health-regulatory situation, FDA's implementation of the "DES proviso" from the early 1970s [Olin *et al.*, 1995]. The risk from extremely small exposures to the undoubted carcinogen DES was held to be negligible, and thus acceptable.

Mathematicians, however, correctly note that "small" -- even "negligible" -- is not the same as "zero." If the statistical-mechanical representation of the process is correct at these small exposures, some nonzero risk will remain. The question now becomes, is this representation exact, so that projections into the "tails" of the underlying distributions are appropriate, or is it only an excellent representation of measurable reality? We have noted that the uncertainties are too large to permit discrimination between threshold and nonthreshold behavior on the basis of quantitative measurements. To examine this issue of low-level behavior, we must take leave of mathematics and reconsider biology.

The evidence suggests that low-level behavior differs. No known biological process is infinite; all are truncated by limits imposed by the physical world. Although the heights of men

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[17] "Safe," that is, from cancer. Some have asserted that this conclusion tells us nothing about safety, generally, because other possible adverse effects have not been considered. Yet for most substances all adverse effects occur at very similar exposure levels, and the very large "margin of safety" required for carcinogens can usually be taken to imply that no other adverse effects will occur if cancer does not. However, exceptions that test this rule are known.

can be well represented by a normal distribution, and thus we can predict the frequency of 19-footers, in fact men the height of giraffes can't live. Our arteries won't stand the pressure required to pump blood to a brain so far from the ground. Similarly, no adult humans are smaller than about thirty inches. The distribution of heights is truncated, not infinite. As we argue below, the science of biological control suggests that these apparently stochastic processes are not really random but truncate at small exposures.

The proposition is made that stochastic processes require that dose-response curves describing such processes have no threshold. But we find that this proposition actually stands on an assumption that is not consistent with our other observations of nature. It assumes that mathematical formulas that describe what can be observed will correctly describe what cannot be observed. The choice of mathematical models used to extrapolate from the observable region into the void is ultimately arbitrary. Without a strongly supportable underlying theory, we can have little confidence that the extrapolation represents reality. In this case, there is no such theory.

There exists no reliable scientific evidence that supports the "no threshold" theory to the exclusion of the "threshold" theory.

SCIENTIFIC EVIDENCE FOR THE EXISTENCE OF A THRESHOLD

In the previous section we examined the arguments supporting the "no threshold" proposition, concluding that the evidence is equivocal and that support for the proposition is based on arbitrary, insupportable assumptions. Here we turn attention to conclusions that can be drawn from modern biological theory. We review first the major change in the theory of carcinogenesis that occurred about 1980, and its implications. Next we review findings from

biological control theory that have emerged in this same time period. Together these two theories strongly constrain the mathematics used to model dose-response for cancer and other kinds of injuries.

- **The current theory of carcinogenesis holds that two kinds of processes can be involved in the development of cancers**

In 1981, Moolgavkar and Knudson described a theory of cancer that is capable of rationalizing essentially all that is known about this disease. (Greenfield, Cohen, and Ellwein [1984] independently developed essentially this same theory at the same time; the mathematical formulations of the two are different, and complementary.) This new theory unified the two long-contending theories of carcinogenesis, somatic mutation and uncontrolled growth, into a coherent whole. It recognizes the requirement that heritable change in a cell's genotype must occur for a carcinogenic transformation to occur, and also recognizes the importance accelerated cell division (mitosis) has for increases in the rate at which such mutations occur. Cancer is much more likely to develop in tissues undergoing rapid growth, both because division must occur to "fix" DNA damage as a mutation, and because a shorter interval between divisions may increase the likelihood that DNA damage will go unrepaired. Thus we can understand why cancers that occur only in childhood (*e.g.,* retinoblastoma) are found in tissues that stop dividing early in life, why rates of sex-organ cancers exhibit an age-dependence that follows growth and development of these organs (rates increase dramatically following puberty), and why "promoters" that do not affect mutation rates can nevertheless greatly speed the development of cancers. The classical somatic-mutation theory cannot by

itself rationalize any of these observations [Moolgavkar and Venzon, 1979; Moolgavkar, 1983; Wilson, 1989; Preston-Martin *et al.*, 1990].

In the last decade there has been an extensive exploration of the implications of this theory, mainly by groups associated with Suresh Moolgavkar at the Fred Hutchinson Cancer Center, Sam Cohen at the University of Nebraska, and Curtis Travis at Oak Ridge National Laboratory. They have used mathematical modeling to explore the relative impact of mutagenic and mitogenic (cell-division rate) effects on the development of cancers, using data from both human experience (*e.g.*, uranium miners) and animal experiment (*e.g.*, saccharin, liver-tumor-promotion) [Moolgavkar *et al.*, 1990, 1993; Ellwein and Cohen, 1988; Cohen and Ellwein, 1990; Travis *et al.*, 1991]. They have consistently found that, unaided, exposure to purely mutagenic conditions does not accelerate tumor formation very much. Purely mitogenic stimuli can significantly accelerate tumor formation, acting most strongly on the mutant, partially transformed cells that exist in all animals by the time of birth [Cohen and Ellwein, 1990]. However, the two kinds of effects act multiplicatively: tumor response rates increase dramatically in exposure regimes where both mitogenesis and mutagenesis occurs. These findings have a number of other interesting implications for public policy (notably concerning how chemicals should be tested). Important for this present discussion is that there are two different physiologic processes, interference with which can increase cancer risk. [18] Of the

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[18] Strictly speaking, at exposure levels capable of causing observable increases in cancer incidence, these two effects interact, with increasing mitotic rate leading to an increased mutation rate (because of less effective DNA repair.) However, at "environmental" exposures, the two effects can be distinguished.

two, speeding up cell division is quantitatively much more important than increasing the mutation rate [Cohen *et al.*, 1991].

- **Mitogenesis is under strict biological control. The DNA damage repair rate appears also to be under close control. This implies that both cancer-causing processes have thresholds.**

In this section we argue that the threshold in exposure-response curves arises from the existence of biological controls on both cell division and DNA repair rates. The mechanism by which mitogenesis is controlled comes primarily from outside individual cells (and thus cannot be understood from studies confined to the cellular level). The control on DNA repair is poorly understood; the existence of such control is inferred from several observations. We start with a few observations on control systems, noting the characteristics that necessarily imply the existence of a threshold in the "controlled parameter". This is followed by descriptions of the control systems for mitogenesis and DNA repair, that lead to conclusions about their exhibition of thresholds.

Characteristics of Control Systems

Control systems strive to maintain some parameter or variable within "control limits" that are set externally to the system. (The simplest control systems employ only one limit, often called a "set point.") Parameters commonly controlled are temperature, pressure, and chemical composition or concentration. Three features are characteristic of this kind of control system: some means by which an actuator can affect the parameter to be controlled; a means by which a controller can sense the state of the system (usually by measuring the controlled parameter) and compare it to the control range or set point; and a means of signaling the

actuator to take action to bring an out-of-control situation back within the control range. The means of sensing the state of the system, which involves the transfer of information from the system to the controller, is called a "feedback loop."

To aid understanding these characteristics, consider the commonplace system that we use to keep our living spaces warm in cold weather. We employ some sort of heater that is cycled on and off by a controller called "thermostat." We identify the air temperature we wish to maintain -- the set point -- and adjust the thermostat so that when the air temperature drops below this point, the device signals the heater to turn on. When the air temperature is warmed above this point, the controller turns the heater off, returning the actuator to its normal state. In this example, the thermostat includes a means to sense when the air temperature needs correcting, by comparing it with the set point, and also a means to convey that information to the heater (in the form of an electrical signal); the source of corrective action is, of course, the heater. In this case, the feedback to the controlling thermostat occurs in the form of an increase in the air temperature.[19]

Note that the heater has some limit on its capacity to add heat to the living space: its "full blast" rate. As long as the heat loss rate is less than the maximum output of the heater,

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[19] Note that this system is not capable of precise control of temperature. It is a one-way system: as long as the inside air temperature is above the set point, the controller does nothing. (If we want to cool the inside, we turn on an air conditioner, and typically use another one-way controller to manage against a maximum set point instead of a minimum.) The common furnace/thermostat system relies on passive heat loss to a cold outside to provide a gradient against which it can work to control the temperature. In houses, this loss rate varies too much from place to place and time to time to allow precise control, but we don't pay much heed to the variability. In situations that require precise temperature control, the systems must provide both a two-set-point controller and ways to regulate both heat input and withdrawal from the environment being controlled.

this system will maintain a constant air temperature. But should the weather turn very cold and windy, and the rate of heat loss exceed the capacity of the heater, the air temperature will begin to drop below the set point. Were we to plot, say, the outside air temperature (holding wind speed constant) against the interior air temperature, the resulting curve would describe a threshold: a straight line of zero slope to that point where the heat loss rate equals the capacity of the heater, after which the interior temperature would decrease proportionately to any further decrease in the outside temperature (Fig. 1).

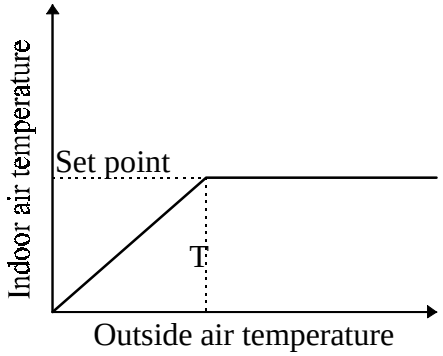

Figure 1

Threshold behavior is intrinsic to and necessary for a system that controls some function or parameter within limits and has capacity to accommodate to external conditions. As long as the external stress is less than that capacity, the controlled parameter will remain constant; when stress exceeds adaptive capacity, adverse effects will begin to occur. Demonstrating that a system is under physiological control is sufficient to show that a threshold will exist in any relationship between measures of its state and measures of external stress.

Biological Control Systems

Biological control systems work in almost exactly the same way as the mechanical system just described. For instance, the central controller of body temperature (thought to be in the hypothalamus) responds to an increase in internal temperature by causing surface blood vessels to expand and by causing sweat to be released, both of which increase the rate at which heat is lost from the body. Instead of electrical signals, the body's central controller uses changes in the concentration of regulatory chemicals (many of them hormones) to signal the need to expand or contract capillaries, *etc.* (Excepting temperature, all biochemical signaling

occurs by means of gradients in the concentrations of various chemicals.) We maintain a near-constant body temperature (within limits) with this system, but it can be overcome: there are limits on the heat load any individual can tolerate before body temperature rises, with consequent adverse effects. This limit is the threshold.

Note that control of body temperature is quite precise. The hypothalamus must contain some sort of two-way controller. The rate at which we produce heat is variable, controlled by the amount of circulating thyroxin, the thyroid hormone. Our capacity to adjust to the external environment is obviously limited in both temperature directions: there exist two thresholds in the curve that relates internal body temperature to the external environment temperature (Fig. 2).

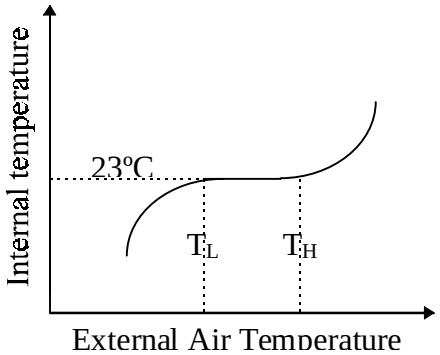

Figure 2

There exist regulatory systems that do not act to maintain a controlled parameter within specified limits. For instance, a system might alter a parameter by some specified ratio or proportion. In industrial practice, such a device could be used for sampling, for instance, taking one can of beer out of every thousand that pass through a packing line. An example from electronics would be a device that takes an incoming signal and reduces its amplitude by some fraction before passing it on. Clearly such a system will have a capacity limitation, similar to that of a typical control system. An inflection point

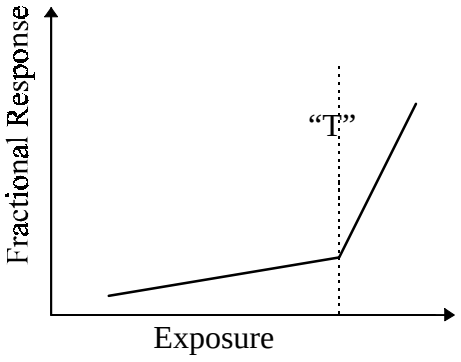

Figure 3

analogous to a threshold could be observed. However, the dose-response expected for a toxicant acting by perturbing such a system would be a "hockey stick," with a nonzero slope below the inflection point followed by a steeper straight line until saturation begins to set in (Fig. 3).

Hormonal control

Our bodies include control systems, that act on every physiologic function. Most if not all involves hormones, the specialized chemicals synthesized in the "endocrine" organs (pancreas, thyroid, hypothalamus, *etc.*) and released directly to the blood. None of these systems is understood completely, and evolution has ensured that complex interactions among them are the norm. Typically control does not reside solely within a single organ, but is shared. For instance, the pancreas increases the rate of insulin release in response to an increase in blood glucose, a decrease in blood insulin, and also in response to poorly-understood signals coming from the intestines by way of the hypothalamus. (Insulin release increases in response to food, just before blood glucose begins to rise.) Control precision is increased by the liver; blood flowing through the liver exits containing less of all hormones than when it entered. Since signals consist of concentration gradients, this creates a constant "sink," comparable to the heat sink of a precise temperature control system, permitting fine control. As a consequence, hormones are continuously released to the blood stream.

Some mitogenic carcinogens act by perturbing hormonal control systems. For instance, they may act by increasing the rate of hormone destruction by stimulating enzyme activity. "Dioxin" and many other chlorinated hydrocarbons increase the activity of a mixed-function oxidase that destroys thyroid hormone, leading, at high enough exposures in rats, to

enlargement of the thyroid (goiter). In rodents, goiter predisposes to thyroid follicular cell cancer (people question whether it does so in humans.) Other chemicals act by interfering with hormone synthesis: thiourea and its analogues act by tying up one of the key enzymes in the synthesis of thyroid hormone, which also leads to goiter and thus thyroid cancer in rodents. "F.D.&C. Red Dye #3" causes the same response by interfering with a different enzyme [Olin *et al.*, 1995]. Estrogen mimics increase endometrial and breast cancer risk by directly stimulating cell division [Preston-Martin *et al.*, 1990]. A progesterone antagonist might have the same effect, at least in the endometrium, since this hormone counteracts the growth-promoting effects of estrogen in this tissue.

Elsewhere [Wilson, 1995] I have derived from basic biochemistry and physical chemistry the nature of the dose-response for these effects; the typical curve is illustrated in Figure 4. This work showed that the equations describing the effects of chronic treatment with any substance that acts by perturbing a hormonal control system include a variable that does not depend on the toxicant dose, generally related to the variable on which the control system works. (For example, in the case of an insulin mimic the effect of which would be reduced blood glucose, the rate at which glucose enters the blood stream is independent of treatment.) The magnitude of this independent term determines the magnitude of the threshold. This work demonstrates that the existence of a

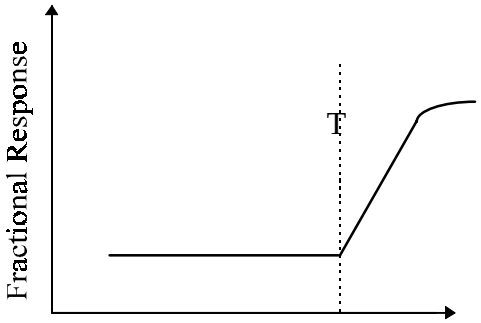

Figure 4

threshold is independent of the mathematics of receptor binding, and that it is a consequence of the existence of control itself.

Control of mitogenesis

The system that regulates cell division and differentiation is now becoming reasonably well understood. The research leading to this understanding has been driven by the discovery that mutations in the genes that code for the many proteins involved in intercellular signaling -- "proto-oncogenes" -- lead to cancer [Weinberg, 1989]. A theory of the control system has been described by Freeman and Wilson [1990]. We know that the key features of control systems exist: a means to sense if control action is needed, a means to transmit this information to a source of the needed action, and a capacity to act.

This control system is very complex, including two separate kinds of signaling pathways, one of which signals "divide," the other signaling "stop." In addition, each pathway includes redundancy and modulation possibilities. For instance, in cells programmed to divide throughout life, such as the stem cells of skin and intestinal lining and of the blood system, both pathways are at least doubly redundant, and three mutations are necessary to convert a normal cell into a first-stage cancer cell [Moolgavkar and Luebeck, 1992]. The primary signal transmitters come from a group of loosely similar large proteins called "growth factors" (*e.g.*, "epidermal growth factor" and "transforming growth factor-beta," or TGF-ß), some dozens of which exist. Other substances, including estrogen, progesterone, insulin, and thyroid hormones, cyclic adenosine monophosphate (*c*AMP), the Vitamin A derivative retinoic acid,

and many others modulate the signals carried by these growth factors.[20] An increase in estrogen concentration increases the likelihood that certain breast cells and the cells of the endometrium will divide; increase in retinoic acid decreases that likelihood. However, control of mitogenesis appears to differ from the temperature control examples above in not having a central controller analogous to the thermostat/hypothalamus. This may be a system best characterized as having "distributed control," in which many system components independently possess the ability to sense a deviation from the control limit and act to restore the system to normality. Individual cells capable of division possess the capacity to sense when division is required. At least some of the growth factors, including TGF-ß, also form part of this surveillance system [Freeman and Wilson, 1990].

Mitogenic carcinogens can increase the cancer rate either by directly increasing mitotic rate in an affected tissue, or indirectly, by suppressing normal growth and thus providing an environment in which mutant cells can then grow. Included in the first category are estrogen and its mimics; classical "promoters" such as phorbol ester, that mimic natural intracellular messenger molecules; and substances that kill cells (*e.g.*, chloroform.)[21] "Indirect" mitogens include "dioxin," which stops the growth of skin and related tissues, and phenobarbital, *N*-2-fluorenylacetamide ("2-AAF") and many other chemicals that stop division of rodent liver cells; continuous exposure to these kinds of carcinogens permits growth of mutant cells that do not respond to "stop" signals and thus are already one step along the road to cancer.

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[20] Both the "growth factors" and modulators can be tissue-specific. Thus estrogen and progesterone act primarily on reproductive-system tissues such as breast and endometrium.

[21] Tumors have long been known to be associated with scars: the cell division essential to healing provides an increased opportunity for the mutation needed to start a cancer.

Thus mitogenesis fulfills all the conditions of a control system: there exist a controller (in this case, "distributed" among all cells capable of division), means of sensing the state of the system (*i.e*., whether to divide or not), means of transmitting signals, and means to effect desired changes. We know from a wide variety of observations that cell growth is strictly regulated. Thus it follows that all dose-response curves for mitogenesis exhibit a threshold.

Recall that the threshold question concerns the response of the control system to small externally-derived stresses. For mitogenesis such stresses would consist of influx of a chemicals that influence internal signal transmission, such as phorbol ester or TCDD, or of the proteins that are released when another cell dies, which increase the propensity to divide [Freeman and Wilson, 1990]. We showed above that dose-response data are themselves too noisy to permit discrimination between "threshold" and "no threshold" models. The biological theory just recounted conclusively demonstrates that for carcinogens which act by increasing the rate at which certain cells divide, robust and redundant control mechanisms require a threshold. For such substances, scientific theory now recommends a policy that treats them in the same way that other serious toxicants are treated. As noted, EPA has begun to do so [EPA, 1996].

Control of DNA Repair

We postulate the existence of a system that controls DNA repair mainly from indirect evidence, of three kinds. First, some of the components necessary for a control system are known. For instance, the enzymes that sense DNA defects and repair them provide a mechanism by which such control can be effected; defects in the proteins involved are observed to be associated with an increased risk of cancer. Second, interspecies comparisons show that

efficiency of DNA repair varies, with longer-lived species (*e.g.*, sea turtles) having very efficient repair while short-lived species (*e.g.*, mice) tolerating much more DNA damage. That we do not protect and repair DNA as effectively as turtles suggests there is an evolutionary advantage to maintaining some level of DNA alteration in the population. If so, there must be some means of controlling the rate. Finally, cancer rates are not sensitive to the altitude at which people live, even though DNA damage rates increase with altitude due to increased cosmic-ray flux. This suggests existence of some constant-rate control system for this parameter.

The existence of a DNA repair system capable of exercising control is necessary but not sufficient to demonstrate existence of a control system. That is, we know that DNA repair enzymes can both sense "out of control" situations and effect a return to the set point. There exists "reserve capacity" to repair damage that can be induced when the DNA-damage rate increases, also a necessary part of a control system. However, not enough is known to understand these processes in control-system terms: in particular, we don't seem to know the location of a controller for DNA repair, and we don't seem to understand what signals the need to mobilize the reserve DNA damage repair capacity.

Not knowing how DNA repair is controlled also means that it is not at all clear how this system may function to permit a constant rate of DNA damage to persist in cells that enter mitosis. There clearly exists "fractional regulation": in humans, it includes the antioxidant systems, such as uric acid, Vitamin C, *etc.*, that protect against DNA oxidation [Ames and Saul, 1985]; enzyme systems generally perform this kind function. Regulation of this sort might satisfy the needs of long-lived animals to minimize DNA damage (during reproductive years).

However, fractional regulation of this kind is not consistent with the very reliable observation that cancer rates are not a function of the altitude at which people live. In particular, leukemia, generally regarded as the cancer most susceptible to initiation by radiation, appears to be randomly distributed across the United States. People living at high altitude, *e.g.*, in Denver, are subject to a significantly higher flux of ionizing radiation from cosmic rays and other extraterrestrial sources than are those of us who live near sea level. If repair were not absolutely controlled to a constant background rate, Denverites should exhibit a higher mutation frequency than, say, Philadelphians,[22] and a higher rate of leukemia. Yet death rates for leukemia are the same, on average, in the Rocky Mountain states as elsewhere, even though these states have overall the lowest death rates for all cancers [Millller *et al.*, 1990].

The weight of evidence now available favors the proposition that mutation rates are under physiologic control, *via* control on DNA repair. We observed that evidence for the "no threshold" proposition for mutagenic carcinogens was vanishingly weak: that derived from study of exposure-response curves is limited by ability to distinguish between "threshold" and "no threshold" behavior at low exposure levels; arguments based on "additivity of exposure" are tautologous, while those based on statistical considerations rest on an assumption that the available evidence contradicts. The evidence favoring the "threshold" proposition is noisy and not terribly strong, deriving primarily from observations consistent with DNA repair being under physiologic control. We might express our confidence in the correctness of the "threshold" theory in terms of odds in its favor; if so, these odds would probably be no better than 3:1.

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[22] Information on mutation frequencies in humans is beginning to become available from different parts of the country. When enough has been done, a more direct test of the postulate can be carried out.

Nevertheless, available science provides more support for threshold-based policies for dealing with mutagenic carcinogens than for policies based on the "no threshold" assumption.

IMPLICATIONS FOR POLICY

In this section, we examine policy implications of the scientific theories described above. Note that the context for this discussion remains small exposures to carcinogens, the arena in which scientific uncertainty is relatively high. Where exposure to carcinogenic chemicals is large enough to expect directly-observable increases in cancer rates, there is no need to resort to extrapolation away from the observable range in order to understand the implications of policy choices. We have noted that few "no threshold" policies are actually followed; the Delaney Clause for food additives and colors, and certain pesticide residues, and the dormant OSHA "cancer policy" are the most prominent among these exceptions, at least in this country. Although in principle they are based on the "no threshold" theory, in reality most regulatory policies rely on the "practical threshold" -- the basis for "*de minimus* risk," "no significant risk," and "negligible risk" decision criteria. We noted that EPA has begun to implement threshold-based policies for some mitogenic carcinogens [EPA, 1996].

1. At low exposures, mitogenic (nonmutagenic) carcinogens should be treated the same as other systemic toxicants.

EPA's evolving policy is fully supported by current scientific understanding of how exposure to mitogenic substances increases cancer risk; it follows from cell replication being under robust biological control. This policy is now limited to a few well-studied cases; it should be generalized to apply routinely to all chemicals that do not exhibit mutagenic activity in a standard test battery.

It should be noted that tests for mutagenic activity are not absolute, in that these tests have a characteristic detection limit. Substances that do not exhibit activity in these tests could actually affect DNA, but have an undetectably small specific activity or potency. Some may argue that because we can't be absolutely sure that substances are not mutagenic, policies should not assume that no activity exists. However, we noted above that mutagenic activity contributes much less to cancer potency than does the mitogenic activity. For those substances that have undetectably small mutagenic activity, neglecting this contribution will make no change in our confidence that sufficiently small exposures cause no harm.

2. At low exposures, risks from exposure to mutagenic carcinogens should be managed based on a "practical threshold" assumption.

Protectiveness of "practical threshold" based standards

Most risks from exposure to carcinogenic substances are now managed using some "practical threshold" approach. It is important to ask two questions of this kind of approach. One concerns the degree of protection actually afforded by this kind of approach. The other concerns what we actually receive from absolute, Delaney-style bans *versus* the practical threshold. We suggest that the benefit from a ban comes from reducing uncertainty that the control measures will actually prevent any injury. Yet there are costs associated with choosing absolute policies. Because "no significant risk" and similar approaches can reduce this uncertainty to extremely small values, policy makers need to give very careful consideration to these costs, especially the indirect ones.

We concluded above that the weight of evidence favors a threshold for all cancer-causing processes, but that there is considerable uncertainty in this conclusion. We noted also

that under the conditions of concern in "environmental" regulation, the very small numbers of active molecules available to attack susceptible cells becomes so small that we can be quite certain no cancer will result, even from a lifetime of exposure. Crudely, the "one in a million" standards conventionally set for exposures to mutagenic carcinogens represent >99% confidence of no injury occurring in populations numbering tens of millions of people, even if there is no threshold. Our confidence in "no injury" is then further increased by the likelihood that a threshold exists.[23]

A ban presumably gives us 100% confidence that no injury will occur from exposure to the banned substance. The practical-threshold approaches provide a >99% confidence that no injury will occur. Thus the difference between the two policies lies in this small (and not accurately measurable) difference in confidence that no one will be hurt.

Considerations on the value of bans: the case of Delaney

The utility or value of the reduction in uncertainty obtained thereby can be judged only by comparison with the benefits that may be foregone by a ban. This is clearly a societal value judgment, not science.

Taking pronouncements of Congress to represent the values of the American public, we can confidently conclude that for many substances and circumstances, the losses that would accompany a ban are considered to exceed the value of the uncertainty thus reduced. For instance, wastes from industrial production that become air and water pollutants must meet the

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[23] These "plausible upper bound" standards calculate a 95% upper confidence limit on response, so, because these are very small numbers, the nominal likelihood of injury in a single representative individual is $<2 \times 10^{-8}$. Taking 2:1 odds against "no threshold," the likelihood drops to $< 10^{-8}$. At such odds, likelihood that no cancer will occur even in a population of 100 million people is more than 99%.

negligible risk standard; carcinogenic animal drugs must meet a similar standard. Industrial chemicals regulated under TSCA are regulated under a different kind of standard in which "unreasonable risk" is the operative term; this standard requires comparing the costs and benefits of a ban with other management alternatives, and may be more or less stringent than the "negligible risk" standards. Since the mid-1960s Congress has considered the benefits of only one class of substances so low as to deserve a ban -- PCBs -- and has excepted saccharin from the Delaney ban.

From all accounts the understandable dread of cancer played a large role in passage of Representative Delaney's successive amendments to the Food, Drug, and Cosmetic Act. At the time these bits of legislation passed, there existed a widespread sentiment that carcinogens "just should not be part of the food supply" [Fleming, 1960]. This sentiment presupposed that carcinogens were rare; now we know that they are common. Combined with public health professionals' belief that no level of exposure could be considered safe, Delaney appears quite a rational policy. Dread of cancer remains. (The supposition that carcinogens were few supported the view that little of value would be lost from a ban on all carcinogenic additives.)

Yet the food additive and food color Delaney standards impose some rather high societal costs. These costs occur as a result of agencies flouting laws that make no sense (to those who staff these agencies). We noted that Delaney represented an unnecessary addition to the food additive laws that removed policy discretion from FDA and EPA and seriously curtailed their scientific discretion. This has caused considerable difficulty as more and more substances have been subjected to tests for carcinogenicity, and found "positive." Many otherwise innocuous natural chemicals are found to "induce cancer," in the strict interpretation

of that phrase. Some of these are used as food additives. One such is a principal component of the oil of oranges and lemons, *d*-limonene; if ingested by male rats in sufficient quantity, kidney cancers develop. *D*-limonene becomes a direct food additive by virtue of the process used in reconstituted orange juice, and it was recently approved by EPA as a food-use pesticide [EPA, 1994]. The scientific community is very confident that these male rat kidney tumors are not predictive of a response in humans, that their appearance means nothing for the safety of d-limonene [Olin *et al.*, 1995]. That confidence was cited by EPA in its approval of the petition to sell the substance as a pesticide. Nevertheless, it seems that, *prima facie*, use of *d*-limonene as a direct food additive and a food-use pesticide both violate the Delaney Clause. Pesticidal use of the chemical is minor, but reconstituted orange juice is a very important product. It should be excusable to suspect that FDA has taken no action, having no wish to provoke a public outcry by banning orange juice.

The *d*-limonene situation provides the most direct confrontation between science and Delaney, but by no means the only one. Several minerals and complex sugars induce cancers in animals, and derivatives of all the essential amino acids and chemicals such as Vitamin C would do so if tested according to the protocol that showed saccharin to be "carcinogenic".[24]

It was not until EPA was challenged over its authority to approve tolerances for "carcinogenic" pesticide residues did Delaney cause more than discomfort among the scientists

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[24] Strictly speaking, most of these have only been tested in a experiment that produces changes in the male rat bladder that are cancer precursors. These precursors are necessary to the subsequent development of tumors, and continued treatment with appropriate test agents has always led to the development of such tumors. Scientists expert in this field, however, are extremely confident that were these to be subject to tests of the design that produces bladder tumors in male rats with saccharin, tumors would be induced.

and policy advisers who had to work around it to satisfy FDA's other responsibilities. In 1986 a National Academy of Sciences committee had criticized EPA for allowing certain old pesticides to remain on the market, even if animal tests showed they may induce cancer, while failing to approve newer, apparently safer ones that were also "possibly carcinogenic" [NRC, 1986]. EPA responded by enunciating a "*de minimus*" risk policy, very similar to FDA's, that would allow it to achieve consistency in pesticide registrations [EPA, 1988]. A California group sued to overturn this policy, successfully, with the result that EPA has moved to cancel many registrations, some of them for pesticides whose absence will harm American agriculture.

A clear consensus exists in the scientific community that use of natural "carcinogens" in food poses negligible or no risk to the public [NRC, 1996]. Nevertheless, strict interpretation of Delaney would seem to prohibit use of any "natural carcinogen" as a "direct" food additive.[25] FDA has not taken action to halt their use, appearing to deal with the dilemma by ignoring the existence of this information. Scientists would approve if FDA has concluded that strict application of the law would harm public health and do no good. However admirable this practice may be, it would seem to have doubtful legality. One might speculate that it has not been challenged because doing so would expose the contradictions in Delaney and its clear obsolescence as policy.

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[25] Since usual food processing techniques seldom cause these to be isolated and then returned to food, as is the case for *d*-limonene in orange juice, these natural carcinogens are considered food "constituents" and not "additives." The Delaney provision then does not apply.

3. "Linear models" for setting numerical exposure standards should be replaced with an equally protective, more transparent procedure.

Both Federal and state regulatory agencies commonly make use of a "linear extrapolation" procedure to derive exposure standards for carcinogens from results of animal tests. These make the assumption that a "plausible upper bound" on the real dose-response function can be approximated by a straight line from test data to the origin. Justification for this approach has been the "no safe exposure to a carcinogen" idea and the somatic mutation theory. As we have seen, this justification is now scientifically very weak, and at least the Federal agencies have begun to use other approaches [EPA, 1996].

At the same time, scientists have shown [Gaylor, 1989a; Krewski *et al.*, 1993] that numerically identical exposure standards can be obtained from the same test data by a much simpler procedure, dividing the estimated 10% response exposure in animals by a factor of 100,000. This parallels exactly the procedure used for "noncarcinogens," the only significant difference being that for noncarcinogens a divisor of 100 is normally employed [Dourson and Barnes, 1988].[26]

This arbitrary divisor is a risk management tool, intended to assure that exposures will be small enough to protect the most sensitive people. Technically, justification for this comes from the irreducible uncertainty of predicting how humans will respond when only information on animal responses is available. It can serve other ends, as well, including policy makers'

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[26] Traditionally, the "no observed adverse effect" exposure is employed as the basis for standard setting for noncarcinogens. The actual response to which this exposure corresponds will vary from test to test, but it is believed usually to be <5%. [Gaylor, 1989b]. Because of the variability in this response, a modified procedure called "benchmark," first proposed by Crump [1984], is now being considered; at least one variant is exactly the same as this one.

judgments that the public wants or needs a greater degree of protection from a particularly dreaded disease such as cancer [*cf.*, Dourson and Barnes, 1988]. Thus the use of a very large "safety factor" can be justified as appropriate policy.[27]

Setting standards by this method, instead of the way they are now set, would have two advantages. First, the process would be much more transparent. Current procedures involve use of a "black box" -- a computer program that very, very few people truly understand or can explain. If essentially the same result can be obtained by a simple, easily understood procedure, public understanding and regulatory agency credibility is served by the simpler one.

Second, it would return to policy makers the ability to trade off uncertainty against other factors that enter into public policy decisions. At present, the decision on how much uncertainty to tolerate lies almost exclusively in the hands of agency technical staff, often isolated from the political process. Science is almost always unable to specify exactly what levels of exposure will be truly "safe," or what disease will occur from particular exposure scenarios. The uncertainties are much too large to allow highly confident statements about these matters. Yet typically policy makers have no way of knowing how large the uncertainties may be. Were it to be recognized that the use of this enormous "safety factor" were convention and not science, an ability to modify it as necessary would flow to risk managers.

The regulatory agencies should give very serious consideration to abandoning their use of these "linear extrapolation" methods in favor of this more honest risk management practice.

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[27] The term "margin of exposure" is sometimes used to express this concept. As this is explicated in the recently revised EPA "cancer guidelines" [EPA, 1996], the practice intended is a comparison between levels of exposure and levels expected to cause harm. Decision makers are expected to decide if this "margin of exposure" is large enough to serve the desired policy ends.

In doing so, however, they should be cognizant of the fact that the risk management practices are the result of a social contract, not managerial whim, and that deliberation about the use and magnitude of these divisors should take place before any final use occurs. Some sort of deliberation including interested and affected parties, informed by input from experts, would greatly increase the likelihood of success.

SOME SCIENCE POLICY ISSUES

The Question of Population Thresholds

So far this discussion has centered on the response of an individual to exposure to a carcinogen. Not all individuals will respond in the same way, and that raises a policy issue for risk management to which we now turn. However, note that because populations are made up of individuals each of whom possesses a threshold of response to any carcinogenic agent, it follows that for any finite population a threshold will exist.

Consider first the case of mitogenic carcinogens. Adaptive capacity in the control mechanism for cell replication gives rise to a threshold in the response to any agent that acts only by affecting this rate. Obviously, different individuals will differ in their adaptive capacity. For a population, the spectrum of differences will be describable in terms of a frequency distribution. There will always exist individuals who are, at any particular time, extremely susceptible to the effects of any stress. We need to ask nontrivial questions: how many of these individuals exist, and how exquisite is their susceptibility? Is there a significant number of individuals in the general population who respond to infinitesimal increases?

Note that the distribution of susceptibilities in the population is likely to be approximately lognormal (number normally distributed as the logarithm of dose) This is

commonly the case for other physiologic functions, and we know nothing to suggest that mitogenic effects may be a special case. If so, the traditional dose-response function will be a probit or other logistic curve [Seabaugh *et al.*, 1991]. This curve, describing the fraction of responders at any particular exposure, drops off very rapidly with decreasing exposure.

Further, the question of perfect versus truncated distributions arises here. As noted above, many biological phenomena can be practically described by a normal or lognormal distribution but the distributions are in fact truncated by physiological constraints. Because real distributions are almost always truncated, it is more plausible than not that the distribution of susceptibilities will also be truncated, and that an absolute threshold will exist in any finite population.

It is also worth noting that there exist processes which, in effect, remove the most sensitive individuals from consideration. Studies of mitogenic carcinogens have consistently shown that mitotic rates must be increased for long periods for any significant risk of cancer to occur [Moolgavkar *et al.*, 1990, 1993; Ellwein and Cohen, 1988; Cohen and Ellwein, 1990; Preston-Martin *et al.*, 1990]. Thus the extremely sensitive individuals must remain in a state in which their reserve control capacity is infinitesimal for a long time. Any individuals for whom this is true must be under severe stress. They must be chronically very ill or very severely malnourished. Practically speaking, most such individuals are either at high risk of death from other causes or their risks from the normal environment are managed by means of hospitalization, or nursing-home care, or other institutional means. The risk management situations that require these very special individuals to be the focus of the kind of analysis

normally intended to apply to the general public will be rare. This does not mean that the possibility can be ignored, but that usually it will not remain as a factor in the policy decision.

Mutagenic carcinogens pose a much more difficult set of policy issues that have not been given the attention they deserve. Two sources of heightened susceptibility exist.

First, it is plausible that the association observed between poor nutritional status (or, more properly, its surrogates, low income or socioeconomic status) and higher rates of cancer death arise from the impact of this condition on the barriers to mutational change discussed above. There exists evidence that these people suffer higher rates of mutation than richer individuals [Jones, 1995].[28] This raises a very thorny issue for policy makers facing site-specific decisions such as air permits for industrial facilities or cleanup levels for a Superfund site near very poor neighborhoods. Should the cleanup levels be reduced to offset their possibly increased susceptibility? This increase is not limited to cancer but relates to all causes of death. Clearly, increasing their income and thus improving nutrition represents the best policy means to improve their health, for stresses arising from site-related exposures are likely to be but a fraction of their total. It is not hard to imagine circumstances in which, given a particular level of expenditure, benefits to the community would be maximized by a minimal cleanup coupled with investments to improve their income. It is beyond the scope of this paper to explore these issues, but further exploration would be useful.

A second group with increased susceptibility to cancer consists of subpopulations whose susceptibility is increased by virtue of inheriting diminished DNA repair capacity. These

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[28] However, results reported by Shaddock, *et al.* [1993] suggest that restricted caloric intake, by itself, does not diminish DNA repair capability.

include some small subpopulations very deficient in one or more kinds of DNA repair (*e.g.*, people with xeroderma pigmentosum, ataxia telangisia, and "fragile X syndrome"), but predominately the (apparently larger) fraction of the population that appears to have somewhat reduced repair effectiveness. These people may bear a high proportion of human cancer [Knudson, 1977, 1995].[29]

Those who are highly repair-deficient cannot be considered part of the normal population because specific risk-management measures must be taken or they die very young. For instance, people with xeroderma pigmentosum inevitably develop malignant melanoma very young unless they absolutely avoid sunlight.

At issue is the larger group, many of whom die of cancer in their 50s and 60s. It is not known if in these people DNA repair capacity is diminished, or their repair *effectiveness* is just less than normal. If it is that their repair effectiveness is reduced but their capacity is normal, minimally elevated exposures to mutagens will not significantly increase their risk. The normal control on mutation-rate will operate. But if capacity is diminished, any extra exposure will increase risk. (More properly, it will tend to increase risk of dying from cancer earlier rather than later.) In principle, this issue can be addressed through research; such research should be given a high priority as this subpopulation is better identified and studied.

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[29] Knudson [1977] states that 70-80% of cancer has some genetic component; about 2% is due to inheritance of certain specific genetic anomalies (such as the "DCC" gene that causes colon cancer) that confer a very high relative risk (100-fold or greater) to developing cancer, either as a child (*e.g.*, inherited retinoblastoma) or a young adult. The remainder may well come from genetic differences that increase susceptibility perhaps 3-fold. If this is so, and about 10% of the population inherits these differences (that are not yet defined or understood), then since about 25% of the population eventually dies from cancer -- a rate that would have changed little this century, were it not for cigarette smoking -- these people comprise most of the cancer deaths [Knudson, 1995]. It seems likely that this more common inheritance occurs as less-effective DNA repair alleles [Loeb, 1991].

"Noncancer" Effects

This paper has focused on cancer but many of the conclusions hold for other kinds of adverse effects. We showed that if toxic substances act by interfering with some physiological process that is closely regulated, such as cell replication, biological control implies a threshold determined by the capacity of the control system to compensate. This conclusion holds specifically for effects caused by substances that mimic or antagonize hormones and related chemical messengers. We note that estrogens and the other sex hormones fall into this class; thresholds exist for the actions of "environmental estrogens." Thresholds will also exist for developmental toxins that act by slowing cell division, as retinoic acid does.

Substances that act by straightforward cell killing also will exhibit threshold dose-response curves. These include strong acids and bases, and also organ-specific toxins such as carbon tetrachloride (liver) and cadmium salts (kidney). There will always exist some ability for tissues to resist these agents, some capacity to absorb damage without killing the cells. In addition, studies on dose-response of substances that accumulate in susceptible tissues, such as lead in nerve cells, may give the appearance of acting by "no threshold" mechanisms. Lead, in particular, interferes with enzymes that play a role in development (among other things). Enzyme systems include spare capacity, and can adjust to stress. Low clearance rates may imply that low exposures cause adverse effects. Observing effects at low exposures simply does not imply that effects will occur at any exposure.

Yet not all toxic responses are of this kind. Some time-sensitive processes, such as mutations in critical control genes, probably are not controllable in the sense we have been using. Mutation-caused developmental toxicity should not be assumed to exhibit threshold

behavior, even though the incidence of such effects is too small to be observed in most cases.[30] Nevertheless, this possibility should not be ignored in evaluating the health risks posed by mutagenic compounds.

CONCLUSIONS

Although "no threshold" has been the accepted policy basis for regulating carcinogens for some forty years, it is based on scientific theories that have been supplanted. Newer theories and results support policies based on the "threshold" theory. The weight of scientific evidence supports the conclusion that there exists an absolute threshold of activity for carcinogens. The only credible evidence arguing that thresholds do not exist, at least for mutagenic carcinogens, relies on an assumption that all the processes that act as barriers to attack by mutagens act as probabilistic barriers, and that the probability distributions are infinite. It is more likely that they are truncated, and that the extra probability of a "hit" resulting in a carcinogenic mutant cell does go to zero at some nonzero exposure. For nonmutagenic carcinogens, there is no credible argument supporting the "no threshold" position that does not also support the "threshold" theory, and a strong basis for concluding that thresholds exist.

There exists a policy question concerning the variability of susceptibility to substances that increase mutation or cell replication rates; if some people have infinitesimal reserve

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[30] Perhaps a quarter of cleft palate cases may be the consequence of mutations occurring in a fraction of the population that carries a defective gene for the growth factors, TGF-α. Inhibiting this growth factor results in cleft palate in mice; the fraction of births in the susceptible subpopulation that results in cleft palate is about that predicted on the basis of background mutation rates [J. D. Wilson, unpublished results].

capacity, it could be concluded that, at the population level, the actual thresholds may occur at very small exposures. Such people must be remembered in doing risk analyses, but managing their risks separately from those of the general population may prove most satisfactory.

We observed that the "no threshold" policy has been largely supplanted by a "negligible risk" policy and see here that the ends implied by the combination of these two ideas can be achieved without making the "no threshold" assumption. Thus this assumption has no remaining policy utility. Since it is not supported by science, it should disappear as a basis for public policy.

Some policy makers may believe that the "no threshold" policy seems to offer them benefits: it makes certain kinds of regulatory decisions almost automatic, or at least much easier to decide than if the risk manager had to engage in the political act of balancing many interests against the uncertainty in analyses of risk. Accompanying this is a cost, borne, as is customary, not by the beneficiaries. It is borne by the scientific community. If policy makers claim that science -- clearly obsolete science -- drives them to make decisions desired on other grounds, science loses credibility. If for no other reason, we in the scientific community should urge that this "no threshold" policy be abandoned. Yet decision makers and the public should also support a policy that can be shown to be based very firmly in well-supported science. Doing so removes a source of confusion that advocates use as a smokescreen to hide their objectives, which are usually value-based. Bringing these out into the open leads to more satisfactory, more accepted, and better public policies.

APPENDIX: HOW SCIENCE CONTRIBUTES TO POLICY FORMATION

One observation made in the course of reviewing this "threshold" / "no threshold" debate is the apparent difficulty people have in separating scientific inferences from policy conclusions This author believes that the difficulty stems in part from scientists' neglect of uncertainty. Science only informs, it does not dictate to policy. Policy makers are perfectly free to ignore scientists' views of the world if they so choose. (Of course, they may look silly having done so, but that's their risk to choose.) Effective policy comes about as a consequence of deliberation among those interested and affected, deliberation informed by analysis of relevant scientific and other information. We distinguish "scientific" information here because Western society has found that it provides a reliable basis for making decisions [Ziman, 1978]. The three distinguishing features of science -- making results public, competition among researchers, and testing theories against sensible reality -- serve to produce knowledge that is more dependable than that produced any other way.[31]

Yet the utterances of scientists, however reliable, should not be mistaken for absolute truth. Scientific conclusions may be the closest approximation to reality available at any one time, but they need always to be regarded as uncertain. Early in this century the logical positivists conferred on science a rarefied status close to absolute truth, but we see things differently today: science is recognized as very much a human activity, with all the limitations that implies. Notwithstanding their usual mode of discourse with nonscientists, among

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[31] We also note that decision makers need knowledge that is beyond the power of science to inform, knowledge concerning values, sentiments, and political realities. These do not fall within the sensible physical world that is the domain of science.

themselves scientists admit the uncertainties that always surround their conclusions. The data on which conclusions are based is always uncertain, the theories used to organize this data are always approximations.[32]

It is very important for policy makers to understand the limits of science in addressing any policy issue. It should be clearly understood that the utterances of scientists are really belief statements: they describe what scientists *believe* to be the best description of nature available at the particular moment.

There exists a very solid basis for having confidence in the practical utility of these beliefs. Over the last four centuries scientists have explored, tested, and hypothesized about all of the physical world that is accessible to study. The fundamental learnings from this study are embedded in and supported by an astonishingly intricate and strong web of observation and theory. At bottom, every strongly supported statement of science relies on thorough checks against physical reality: the more numerous these tests, the stronger the confidence that can be placed in any conclusion. Not all scientific statements are amenable to direct testing (although ingenious experimenters can often find ways to test ones that others think impossible). Our confidence in both those directly testable and those not depends strongly upon the weight of evidence supporting each proposition. A substantial quantity of inferential or indirect evidence can add up to a strongly supportable conclusion.

Perhaps contrary to expectation, confidence in a conclusion is not necessarily the inverse of uncertainty surrounding that conclusion. Scientists may well be highly confident that

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[32] In fact, as Shlyakhter [1994] has shown, even the most careful of physicists tend to underestimate uncertainties.

something is correct within some range -- a "confidence interval." For instance, suppose that some policy decision were to depend on the rate at which white men die from bladder cancer for the next five years. Suppose further that NCI has been measuring this rate for more than thirty years, and that it varies randomly around an average of 60 ± 5 deaths per year per 100,000 adult white males, where the "± 5" corresponds to two standard deviations of the year-to-year variability over the three decades. It is obviously impossible to know what the bladder cancer death rate will be a year or two hence, but we can make a prediction of what is likely to be from the NCI data, and making one prior assumption. That assumption is that no influence will alter the underlying rate for the next several years, *i.e.*, that the past predicts the future. This assumption is consistent with everything that is known about causes of bladder cancer. The policy-relevant *scientific* prediction would then be that the "best estimate" is 60/100,000 deaths per year, with a >95% confidence that the rate will between 55 and 65 per 100,000. Because the year-to-year variability appears to be random, this prediction is uncertain; confidence that it will turn out to be exactly 60/100,000 will be only moderate, but confidence that it will fall within this range will be very high.

The policy options available may not be sensitive to this ~8% uncertainty in the bladder cancer rate. If so, the impact on the decision to be made will be negligible. For instance, in the early 1960s there was very real uncertainty in our measurement of the distance between the surfaces of the Earth and Moon. Yet it was not at all important to the decision to proceed with the Apollo program, and would not have been important even had that uncertainty had been one hundred times larger. At the other extreme the uncertainties may be large enough that any of several policy options would be consistent with the scientific knowledge.

Conclusions from the social sciences are seldom precise enough to constrain very much decisions concerning such important social issues as the increasing rate of teenage pregnancies. Both the theories and observations that can be made include uncertainties so large that they provide little basis for informing choice among policy options.

The science which underlies this "health risk assessment" field ranges from very certain, from the point of view of policy, to quite uncertain. Predictions based on fundamental chemistry and biochemistry are very precise: for instance, all cells are destroyed by strong acids and strong bases. Conversely, predictions based on comparative toxicology may be very uncertain: knowledge of the dose at which any particular chemical causes, say, kidney failure in male rats will not necessarily predict even whether humans will suffer the same effect, let alone at the same dose. (Nevertheless, there are means by which reasonably reliable predictions can be made, for specific decision circumstances.)

Scientists often speak of "weight of the evidence" regarding opposing scientific propositions. This phrase usually conjures up in people's minds the image of the scales of justice, an apt parallel. Howson and Urbach [1989] have convincingly demonstrated that the process of scientific induction can best be described as Bayesian, with evidence for and against any particular proposition translating into greater or smaller confidence in it. Scientists learn this mode of reasoning informally, by apprenticeship, and few understand or apply the underlying theory. Nonetheless, if a fair presentation of the policy-relevant science is to be made, the justification for the way the evidence was weighed needs to be included.

If uncertainty is not acknowledged, as is often the case, we may be presented with "dueling scientists." When the uncertainty bounds do not constrain policy choices, advocates for

one or another of the choices may, often do, select the evidence that favors their preferred option and present it as though there were no uncertainty. Their opponents, not surprisingly, commonly employ the same tactic, selecting information and theory supporting their position. It becomes exceedingly important for scientists to be candid and for policy makers to understand the limitations on scientists' pronouncements. Realistically characterizing uncertainty will not banish the "dueling scientists" phenomenon, but it will empower those who wish to understand the underlying science and the degree to which it can inform a particular decision.

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