Policy Analysis

Cato Institute Policy Analysis No. 263: EPA's Cancer Risk Guidelines: Guidance to Nowhere

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Executive Summary

The Environmental Protection Agency claims that implementation of proposed revisions to its guidelines for conducting cancer risk assessments would result in risk estimates based on the best available scientific knowledge and encourage development of new, relevant science. In fact, the proposed guidelines represent a setback for public health, science, and the EPA cancer risk assessment process.

First, the proposed guidelines would remove the existing requirement that epidemiologic studies be statistically significant before they are relied on to establish cause-and-effect relationships between chemical exposures and cancer.

Second, the guidelines maintain a number of default assumptions that have no scientific justification and dictate inflated risk estimates.

Third, although the guidelines provide for the use of other assumptions under certain conditions, no clear guidance is provided about what kind of data can overcome reliance on the default assumptions. Moreover, adoption of different assumptions may make little difference to risk estimates.

This analysis of the proposed guidelines demonstrates that the EPA needs to move from "how many rats get cancer from massive doses of chemicals?" to "what realistic public health benefits can and should be produced through regulatory programs that cost billions of public and private dollars each year?" Until Congress recognizes the legitimacy of the latter question and holds hearings, arguments about regulatory changes will deal with minutiae while gigantic regulatory costs pile up with no expectation of improvements in public health.

Introduction

The Environmental Protection Agency's "cancer guidelines" tell manufacturers how to test chemicals for carcinogenic and other toxic effects and how the agency will interpret the results of those tests. In some cases, the results have led to regulations and withdrawal of products from the market. Even in the absence of any attempt at regulation, the classification of a chemical as a carcinogen (or as a cause of any other kind of toxic effect) can lead to a dwindling market share for a product and to its eventual withdrawal from the market.

Regulations and reduced markets cost manufacturers and raise prices, and, even worse, they can have adverse health consequences. The National Cancer Institute urges that everyone eat five fresh fruits and vegetables daily to reduce the risk of cancer, and the use of pesticides has contributed to the availability of fresh fruits and vegetables at affordable prices. Bruce Ames, a member of the National Academy of Sciences and a biochemist with a distinguished record in cancer and aging research, has contrasted the good that comes from pesticide use that increases availability of fresh

foods with the harm that is done by the EPA's unnecessary regulation of pesticides that drives up the cost of food production and consumer prices. [1] Ames is especially critical of the EPA's regulations based on tests that show that chemicals cause cancer in laboratory animals because those tests are carried out at such high doses of chemicals that the results are completely misleading. [2]

Such objections have been raised for 20 years. [3] They were raised against the EPA's first cancer guidelines that were published in 1976 and the revised guidelines that appeared a decade later in 1986. [4] The newest version of the guidelines, issued for public comment in April 1996, supposedly responds to the criticisms and provides mechanisms for making better use of science in making decisions about the carcinogenicity of chemicals.

Before turning to those guidelines, which promise more than they deliver, we review the evidence about the role of the environment--in the sense of pollution of air, water, and soil--in cancer causation. The environment plays a tiny role, and the EPA's efforts, even if they achieved all the success that can be hypothesized for them, would have a minuscule effect on cancer rates.

"Environmental Cancer" Isn't What We Thought or Were Told

When the EPA was established in 1970, there was a clear expectation that cleaning up the air, water, and soil would improve human health, and that expectation was alive and well when, in 1976, the EPA published its first cancer guidelines. Now, 20 years later, the latest revisions of the guidelines, "EPA Proposed Guidelines for Carcinogen Risk Assessment," arrive at a time when scientists are almost uniform in their opinion that chemicals in the environment are associated with only a tiny proportion of cancer. [5]

The word "environment" has two very different meanings. John Higginson, the first director of the World Health Organization's International Agency for Research on Cancer, is credited with first saying that the environment caused upwards of 90 percent of all cancers. He used "environment" to include *everything* with which people come in contact. "Environment is what surrounds people--and impinges upon them . . . the air you breathe, the culture you live in . . . the chemicals with which you come in contact." [6] In a 1979 interview with Science magazine, Higginson explained that many people misunderstood the word "environment" to mean chemicals, and he underscored the strong incentive for some people and organizations to have it misunderstood in that way:

> A lot of confusion has arisen . . . because most people . . . have used the word "environment" purely to mean chemicals. . . .
>
> The ecological movement, I suspect, found the extreme view convenient because of the fear of cancer. If they could possibly make people believe that cancer is going to result from pollution, that would facilitate the cleaning up of the water, the air, whatever it was. . . . People would love to be able to prove that cancer is due to the general environment or pollution. It would be so easy to say "let us regulate everything to zero exposure and we have no more cancer." The concept is so beautiful that it will overwhelm a mass of facts to the contrary. [7]

Higginson was right. The idea that environmental pollutants are the cause of much human cancer is very attractive. In the first place, it explains the inexplicable. Although 25 percent of people in the United States will develop cancer at some time during their lives (and about 20 percent of all deaths are caused by cancer), the causes of most cancers remain unknown. Being told that the causes lurk in environmental chemicals makes many people think that we have an explanation for the occurrence of cancer. Second, and even more satisfying, as Higginson points out, if chemical causes can be identified and eliminated, cancer rates should fall.

The evidence that pollution is a common cause of cancer was never strong, but scientific reviews of information about causes of cancer that were published in technical journals had little influence on public policy until 1981. In that year Sir Richard Doll and Richard Peto published their encyclopedic analysis of the causes of cancer, which investigated the evidence for the widely discussed "cancer epidemic" and cataloged the causes of cancer in the United States. [8]

Doll and Peto documented that cancer deaths were increasing among elderly people who, because of reductions in deaths from infectious diseases, heart diseases, and accidents, were living to the advanced ages at which cancer is common. [9] Even so, the percentages of elderly people who died from cancer were not increasing. When allowances were made for the increased number of cancer deaths expected in an aging population and for increases in lung cancers, the age-adjusted death rate from all cancers had not changed over the four decades from 1933, when collection of national data began, through the 1970s, the latest years for which data were available when Doll and Peto did their research.

Mortality from some cancers--especially pulmonary cancers--had increased; mortality from other cancers--especially stomach cancers--had decreased during that period. Many of those changes can be explained. Increased smoking goes along with increased pulmonary cancers; changes in food preservation that reduce the amounts of ingested natural toxic materials and of meats preserved by smoking and salting are associated with reduced stomach cancers. There was no evidence of a surge in overall cancer rates.

More recently, Susan S. Devesa and her colleagues at the National Cancer Institute compared cancer rates in the United States in the 1975 through 1979 period to rates in 1987 through 1991. Cancer incidence rates increased 19 percent in men and 12 percent in women, with almost all the increases accounted for by higher prostate cancer rates in men and higher breast and lung cancer rates in women. The researchers concluded, "Improved detection appears to account for most of the increases in breast cancer among women and prostate cancer among men. On the other hand, cigarette smoking is the major determinant of the rise in lung cancer among women." [10]

Deaths from cancer increased less, 3 percent and 6 percent among men and women, respectively. Those increases were "driven mostly by continuing increases in lung cancer mortality, while death rates for the majority of cancers were steady or declining." [11]

One of the conclusions of Devesa et al. is especially important to any discussion of environmental causes of cancer:

> Increasing exposure to general environmental hazards seems unlikely to have had a major impact on the overall trends in cancer rates, in agreement with the conclusion reached in a recent investigation of mortality trends in England and Wales, although rising rates from certain tumors have been clearly influenced by changing exposures to tobacco smoking, HIV infection, and sunlight exposure. [12]

In editorial comments about the Devesa et al. paper, epidemiologists Philip Cole and Warren Sateren predict that cancer will replace heart disease as the number-one cause of death, as measured by the number of deaths, in America at the turn of the century. [13] Even so, the age-adjusted mortality rate from cancer is decreasing, as indicated by national statistics for 1992. Decreases in cancer mortality are most clear among young and middle-aged people (Devesa et al. report that total death rates from cancer are decreasing in both men and women under age 55). It is expected that the effects of prevention and improvements in treatment that have reduced mortality in young and middle-aged people will accompany them as they age and that age-adjusted cancer mortality will continue to drop.

In their 1981 study, Doll and Peto concluded that "pollution," their term for chemicals in the environment, was associated with about 2 percent of all cancers; "geophysical factors," their term for natural radiation, was associated with about 3 percent of all cancers (Table 1). Those results were far different from the conclusions that had been reached by people who equate the word "environment" with "chemicals," but Doll and Peto's conclusions have become accepted wisdom, and few, if any, people argue today that "cleaning up the environment" is going to make much difference in cancer rates.

Table 1
Percentages of All Cancer Deaths Attributed to Various Factors

	Source of Estimate			
Factor or Class of Factors	Doll and Peto	EPA	Willett	Ames et al.

Diet	35 (10-70)[a]	-	32 (20-42)	20-40
Tobacco	30 (25-40)	-	-	35
Infection	10 (1->10)[b]	-	-	-
Reproductive and sexual behavior	7 (1-13)	-	-	-
Occupation	4 (2-8)	1-4	-	5
Alcohol	3 (2-4)	-	-	-
Geophysical factors (natural radiation)	3 (2-4)	3-6	-	-
Pollution	2 (<1-5)	1-3	-	-
Food additives	1 (-5-2)	-	-	-
Medicines and medical procedures	1 (0.5-3)	-	-	-
Industrial (consumer) products	<1 (<1-2)	<1	-	-
Unknown	?[b]	-	-	-

Sources: Richard Doll and Richard Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," Journal of the National Cancer Institute 66 (1981): 1193-1308; Environmental Protection Agency, Unfinished Business: A Comparative Assessment of Environmental Problems, Appendix I to Report of the Cancer Risk Work Group (Washington: EPA, February 1987), tabulated in Michael Gough, "Estimating Cancer Mortality: Epidemiological and Toxicological Methods Produce Similar Assessments," Environmental Science and Technology 23 (1989): 925-30; Walter C. Willett, "Diet, Nutrition, and Avoidable Cancer," Environmental Health Perspectives 103, supplement 8 (1995): 165-70; and Bruce N. Ames, Lois S. Gold, and Walter C. Willett, "The Causes and Prevention of Cancer," Proceedings of the National Academy of Sciences 92 (1995): 5258-65.

[a]The best estimate is presented, followed by the "range of acceptable estimates."

[b]Doll and Peto considered these numbers very uncertain.

EPA's Estimates of the Effects of EnvironmentalExposures on Cancer Rates

The EPA itself presented data about the minor importance of environmental exposures for cancer rates in its 1987 report *Unfinished Business*, a compilation of the agency's scientific and technical managers' best estimates of the numbers of cancers expected from various environmental hazards. [14] Unlike Doll and Peto, who used only epidemiologic data, the EPA used information from risk assessment projections as well as epidemiologic studies to make its estimates. Even so, the EPA's estimates agreed very closely with those of Doll and Peto; the EPA estimated that pollution caused 1 to 3 percent of cancer compared to Doll and Peto's estimate of 2 percent. Indeed, the EPA's and Doll and Peto's estimates for all the causes of cancer that might be regulated agree, and they are all low (Table 1). [15] Subsequently, Michael Gough, who was then at Resources for the Future, a Washington think tank, calculated that if the EPA's estimates of cancer risks from environmental exposure were correct and if its regulatory programs were 100 percent successful in controlling those exposures, the agency could eliminate between 0.25 and 1.3 percent of all cancers. [16]

The Effects of Food-Borne Carcinogens

Much of the population's exposure to environmental carcinogens, whether in food additives, food packaging, or pesticides or as airborne pollutants that deposit on foodstuffs, is through ingestion. How big is the risk? In 1992 Werner K. Lutz, a toxicologist at the Swiss Federal Institute of Technology, and Josef Schlatter, in the Division of Food Science at the Swiss Federal Office of Public Health, calculated the total cancer risks imposed on the population of Switzerland by the ingestion of chemicals in food. [17] They concluded that alcohol was far and away the substance associated with the most cancers, about 8,000 cancers per million Swiss. All other chemical carcinogens could account for no more than a few hundred of the 200,000 or so cancers expected in every million people. (Overeating, which is associated with increases in some cancer rates, was the largest risk from food; Lutz and Schlatter calculated that "overnutrition" accounted for 60,000 cancer cases per million people.)

A committee of the National Research Council underlined the minor role that ingested carcinogens play in cancer causation:

> First, the committee concluded that based upon existing exposure data the great majority of individual naturally occurring and synthetic chemicals in the diet appear to be present at levels below which any significant biologic effect is likely, and so low that they are unlikely to pose an appreciable cancer risk. [18]

Cancer, the Environment, and Regulations

There are about 530,000 cancer deaths annually in the United States. According to the EPA's estimate, pollution causes 1 to 3 percent of cancer deaths, or between 5,300 and 16,000 deaths annually. According to Gough's estimate, EPA regulation, if it works perfectly, can prevent between 0.25 and 1.3 percent of cancer deaths, or between 1,300 and 7,000 cancer deaths. Environmental exposures account for only a tiny fraction of cancers, and EPA regulations, if perfect, can reduce cancer rates by no more than about 1 percent. In fact, regulations of pesticides may do more harm than good because a diet rich in fresh fruits and vegetables protects against cancer, and pesticides make fruits and vegetables less expensive and more available. [19]

That information is far different from what was "known" 20 years ago when the EPA issued its first cancer guidelines. Does the knowledge that the environment plays little role in cancer make any difference to the new guidelines? No. Can we expect that such knowledge will ever make a difference? Yes, if scientists and public health experts can convince Congress to reconsider the EPA's mandate and to investigate the underpinnings of expectations that regulation of environmental carcinogens will improve public health.

Fundamental to rethinking the EPA's role in cancer prevention is a willingness to address the differences between science and risk assessment. The EPA touts its draft guidelines and risk assessment processes as "science-based" and incorporating the "best science." Both claims have enormous political advantages for the EPA. Either claim removes risk assessment from the policy arena and sets it up as an issue to be left to "technical" or "science-based" organizations like the EPA. The EPA has every incentive to use that cover to increase its regulatory reach and to avoid opening its draft guidelines and processes to the criticism of being policy driven.

The EPA also has every incentive to sprinkle "public health" throughout the new guidelines to justify its expensive, disruptive, and, perhaps, disease-causing regulatory program.

Science Is Hypothesis and Test

Risk assessment is not and cannot be science (although it can be done better than it is now). [20] The late Karl Popper remains the most influential philosopher of science, and his description of science as a two-stage process satisfies most scientists. Science advances by first developing ideas or hypotheses or theories, any of which is a tentative description of reality, and then testing them. It is the second step that sets science apart from other kinds of knowledge. [21] The physicist Paul Davies put it this way:

> A powerful theory is one that is highly vulnerable to falsification, and so it can be tested in many detailed and specific ways. If the theory passes those tests, our confidence in the theory is reinforced. A theory that is too vague or general, or makes predictions concerning only circumstances beyond our ability to test, is of little value. [22]

Risk Assessment Is Hypothesis without Test

The basis of a risk assessment is observations about adverse health effects in test animals or in highly exposed people under certain specified conditions, and its product is a hypothesis about health effects to be expected in humans under other exposure conditions. Only rarely, if ever, can such hypotheses be tested.

Some cannot be tested because the person who is deemed at risk does not exist. In the past, EPA risk assessments considered risks to the "maximally exposed individual." As a generalization, the MEI was a hypothetical individual who lived at the point of maximum exposure on the fence line of a factory. The MEI never went to work, to school, or on vacation; he never entered his own house but remained outside for 70 years in the thickest part of the plume of pollution that streamed from the plant. There never was such a person. More recently, the EPA has given up on the MEI and makes more realistic assumptions about exposures, but more realistic exposure scenarios do not make it possible to test the risk assessment predictions.

Risk assessment predictions cannot be tested because the predicted rates of illness or death are so small that they cannot be detected. [23] The product of a cancer risk assessment is an estimate of how much cancer is expected from exposure to the assessed agent. As a rule of thumb, carcinogen exposures associated with less than a one-in-a-million increase in lifetime cancer risk are regarded as acceptable. Anything higher than that is likely to be regarded as meriting attention, including regulation. It would appear that such a fundamental dividing line should have been decided by Congress, but it was not. In fact, no one knows where it came from. [24] The persistence of that number, which has no objective basis, is probably illustrative of the role of emotion in environmental policy.

No one can measure an increase of a one-in-a-million lifetime cancer risk, which is equivalent to about three cancer cases or deaths per year in the United States. [25] The increase is simply too small to be seen against the background of cancer present in our society. [26] Likewise, no one will be able to see the results of a regulation or some other reduction in exposure that reduces risk by one in a million.

Risk Assessment at the EPA

The EPA's efforts to estimate cancer risks from chemicals and to regulate exposures to them have little to do with public health and everything to do with the viewpoint that manufactured chemicals are a plague and that the world would be a better place were they eliminated.

Public health is concerned with such things as the eradication of smallpox and that of polio, which is expected early in the year 2000. It is concerned with the control of infectious diseases that can be spread through air, water, and food. It is concerned with clearly established links between causes and diseases, sick people, and deaths and with investigations to establish the existence of such links or interventions to sever them.

The EPA's cancer assessment is not concerned with such concrete events. Rather, it is concerned with hypothetical cases of disease that may or may not be associated with environmental exposures to chemicals. It also differs fundamentally from public health in that the costs of regulatory intervention to control the hypothetical risks are far, far higher than the costs of controlling other sources of disease.

Tammy O. Tengs and her colleagues at the Harvard Center for Risk Analysis examined the costs of 500 "life-saving interventions," which were defined as "any behavioral and/or technological strategy that reduces the probability of premature death among a specified target population." [27] They calculated that the median cost of an intervention for each life-year saved was $42,000, with an enormous range: the median cost of a medical intervention to save a life-year was $19,000; the median cost of injury reduction was $48,000; the median cost for toxin (chemical) control was

$2,800,000, fully 83 times higher than the average of the medical and injury interventions. Most of the examined toxin control measures were directed at carcinogens.

Not surprisingly, given the EPA's focus on toxin control, its regulatory programs are the most expensive of studied federal regulatory agencies: the EPA forces the expenditure of an average of $7,600,000 per life-year saved as compared to the Federal Aviation Administration's average regulatory cost of $23,000 per life-year. [28]

Despite the weakness of the argument that EPA regulations protect public health, the agency uses it to justify its regulations, and the EPA can be expected to use that justification to trump any attempt to force significant change in its risk guidelines. The EPA has adopted a series of "science policy" assumptions to guide its interpretations of its risk assessments. Those assumptions include flat statements that (1) animal test results predict human risk and (2) toxic effects seen only at high dose levels in animals are predictive of human risks at far lower exposure levels. Those assumptions shift the burden of proof away from the EPA. The agency does not have to demonstrate that humans are at risk or that its evidence indicates human risk at low exposures. Instead, anyone who opposes its interpretations has to demonstrate that the EPA errs. That might be a tolerable burden, but the EPA, as shown in the draft guidelines, decides what opposing information it will consider. Even if the EPA were open to serious consideration of opposing information, no one has ever determined how many observations and facts are necessary to displace an assumption.

We expect that the new guidelines, if adopted as drafted, will make little difference. The alternative is to initiate a serious analysis of the contradictions between the EPA's assumptions and available knowledge and information. Without that analysis and revision of the draft guidelines, little will change, and fundamental questions about whether the low risk from environmental exposures justifies any guidelines or regulations at all will be left unaddressed.

The 1996 "Cancer Guidelines"

According to EPA officials, the new draft guidelines differ from earlier ones in that they are less prescriptive and encourage the development and application of new tests for carcinogenicity and new approaches for analysis of test results. [29] That sounds good, but the devil is in the details, and the proposed guidelines reserve so much discretion to the EPA that we expect little difference in risk assessments based on animal tests. On the other hand, without a word of explanation, the EPA proposes a major change in its evaluation of epidemiologic studies. Tests for statistical significance have always been used to guard against the possibility that an apparent association between an exposure and a disease occurred by chance. The proposed guidelines drop any requirement for demonstrating that associations between exposures and human cancer are statistically significant.

The EPA's "Major Changes" from the 1986 Guidelines

We summarize the EPA's four "major changes."

Risk Characterizations. Risk assessments are usually divided into four parts (or steps): (1) The hazard assessment part describes the evidence that a substance can cause adverse effects in humans or test animals. (2) The dose-response part lays out what is known about the relationship between different doses (in animals) or different exposure levels (in humans) and the manifestation of the adverse effects identified in the hazard assessment step. (3) The exposure step describes what is known about human exposures to the hazard identified in step 1. (4) The risk characterization step puts together the information from steps 1, 2, and 3 to estimate the effects of current or hypothetical exposures on humans and the expected favorable consequences of controlling those exposures.

> The first "major change" in the proposed guidelines is
>
> Increased emphasis on providing characterization discussions for the hazard, dose response, and exposure sections . . . [that] serve as starting materials for the risk characterization process which completes the risk assessment. [30]

Risk assessments might get longer or shorter as a result, or they might not change. "Increased emphasis" is hopelessly subjective, and it is impossible to guess whether it will make any difference.

Weighing Evidence of Hazard. In the 1986 guidelines, information about the relationship between exposures and tumors in animal tests or humans was "the dominant [component] of decisions. Other information about an agent's properties . . . played only a modulating role as compared to tumor findings." In other words, if a chemical caused tumors in animals, the EPA could (and often did) brush aside biochemical and molecular biological evidence that the biological events necessary for tumor formation occurred only at very high exposures.

According to the draft guidelines, that will change. In particular, the EPA says it will welcome information about the "modes of action" of carcinogens. Mode of action information could, for instance, include data about different biological responses to a chemical at high and low doses or data about whether an enzyme that is necessary for tumor formation in a laboratory rat exists in human beings. As the EPA says, if the "new kinds of data" are not forthcoming, this "major change" will have no effect.

Certain predictions can be made. The EPA and some environmental organizations will be eager to use new kinds of data that suggest or indicate that a substance is likely to be a human risk, and manufacturers and users of chemicals will be equally eager to use new kinds of data that point in the opposite direction. In any case, the EPA will remain in the referee's chair, deciding which new information to hear and consider and which to reject.

Classification Descriptors. For 10 years the EPA, following the lead of the International Agency for Research on Cancer, has classified chemicals in an alphanumeric scheme that ran from A--substances known to cause cancer in humans--to E--substances for which there was evidence of noncarcinogenicity in humans. In practice, the important substances were those classified as A, B1, or B2. Substances classed as A were known human carcinogens; substances classed as B1 were known animal carcinogens with some evidence of carcinogenicity in humans; and substances classed as B2 were known animal carcinogens with no evidence of carcinogenicity in humans. The EPA calculated a carcinogenic potency factor for each A, B1, or B2 substance, and the potencies were used to set limits on human exposures. Substances rated C and below essentially dropped from view.

The new classification descriptors sound quite different. There are only three--Ã®known/likely,Ã® Ã¬cannot be determined,Ã® and Ã¬not likely.Ã® In practice, it amounts to the same thing: there is little difference between the A, B1, and B2 grouping and known/likely. As it did for A, B1, and B2 substances, the EPA will figure a numerical risk value for the known/likely substances. Risks for other substances will not be calculated.

We say that the new classification will make little difference even though we are astounded that the EPA proposes a single class that will include substances such as asbestos for which there is overwhelming evidence of human carcinogenicity and such things as trichloroethylene for which there is contested animal evidence and essentially no human evidence. That flies in the face of logic. But practically, it marks no change from the way the EPA has always operated.

Dose-Response Assessment. In the past, the EPA used a linear, no-threshold model to estimate cancer risks and generate numerical risk values. That model produces high estimates of carcinogenic risk, a good thing for a regulatory agency looking for regulatory targets and a bad thing for a manufacturer or user of a useful chemical who is subject to the regulations. The model makes little difference to public health because of the very low risks associated with environmental exposures no matter what model is used.

Alternative models do, however, produce lower risk estimates. Nonlinear models postulate relationships between exposure and cancer risk in which risk increases less than proportionally with dose. For example, a doubling in exposure woud result in less than a doubling of risk. Threshold models incorporate the idea that there is no risk at all below a "threshold" exposure.

The new guidelines say that the EPA will use a different risk assessment model, a "nonlinear" model, that will predict lower risks when there is sufficient evidence to choose. The draft guidelines do not make clear how the choice between the usual linear and the new nonlinear models will be made. Moreover, the results of use of the nonlinear model cannot be predicted.

Statistical Significance--The Unidentified Major Change in the Guidelines

Anyone who flipped a penny 10 or 20 times in a row in junior high math class knows that random events do not always appear to be random. Everyone in the class knew that on average there would be 10 heads and 10 tails after 20 flips, but no one was much surprised that the ratio was 11 to 9 or even 15 to 5. In fact, the teacher might have explained, a ratio of 20 to 0 would not be out of the question if enough 20-flip trials were run.

The role of chance is an important consideration in understanding the results of epidemiologic studies. Epidemiologists, especially those who study the possible role of environmental chemical exposures in cancer, are always looking for a tiny effect against a very large background. About 25 percent of the population will develop cancer during their lifetimes; cancer is a common condition. Let us assume that an epidemiologist divides some part of the population into two groups on the basis that one group was probably exposed to more of chemical C than the other group. Quite apart from any impact of chemical C, it is possible that, by chance, cancer will be more common in one group than the other. Various statistical tests have been devised to guard against accepting results that arise by chance as evidence that chemical C increases or decreases cancer rates. The tests are generally lumped together under the rubric "tests for statistical significance."

Statistical significance was a prominent feature of the 1986 guidelines. It is largely absent from the new guidelines, and its former importance as a threshold to be crossed is completely erased. Last year, an article by Gary Taubes in *Science* made repeated references to epidemiologists who cautioned that rigorous barriers have to be maintained against jumping to false conclusions about associations between exposures and diseases. [31] One of those barriers is the use of tests for statistical significance. The EPA's stepping back from requiring statistical significance is a step away from serious standards. In any case, the EPA neither presents nor discusses reasons for dropping a requirement for statistical significance, but the change is probably the most important one in the new guidelines.

Sources of Risk Information

The most certain source of information about cancer risks is epidemiologic studies. Two kinds of epidemiologic studies have produced direct evidence of human cancer risks: studies of workers in certain industries and studies of patients treated with certain cancer-treatment drugs. No epidemiologic study of a chemical in the environment has ever demonstrated an increased cancer risk. The occupational and medical studies produce information about cancer in humans but leave the problem of extrapolating from the high exposures in the workplace or medical practice to far lower environmental exposures.

The backbone of carcinogen identification is the animal bioassay, which is designed to reveal whether or not a chemical can cause cancer in laboratory animals. Once a substance has been identified as a carcinogen in an animal test, two extrapolations are required to translate the information into an estimate of human risk: One involves making projections from the effects of the high dose of the substance that causes cancer in animals to the expected effects at the far smaller exposures experienced by humans. The other involves deciding how well the animal results predict human effects. Those are clearly the critical extrapolations in risk assessment, and much of the new guidelines is a discussion of them.

It has been axiomatic that a substance that does not cause cancer in animals and for which there is no evidence of contribution to cancer in humans is not to be regarded as posing a cancer risk. But the draft guidelines open the door to considering some chemicals suspect even if they are not carcinogenic in humans or animals. The vehicle for those risk assessments is a collection of poorly defined and discussed tests of biological changes in animals or cells or humans that may be reason for some pre-cancer concern. Each of those tests will introduce a new extrapolation step: what is the quantitative relationship between the noncancer effect measured in cultured cells or test animals or humans and cancer in humans?

There is no inherent flaw in epidemiologic studies, in animal cancer tests, or in tests for biological changes. There is no fundamental reason to expect that any of them produces information that is worthless or even misleading for estimating human risks. But a careful reading of the new guidelines reveals the EPA's biases for finding risks, for inflating those risks, and for laying the groundwork for regulations. Those biases influence the EPA's interpretation of all information from all sources.

Epidemiology

The EPA rightly acknowledged that epidemiology, the study of distributions and causes of disease in human populations, is potentially the most valuable tool in risk assessment. We agree. We differ with the EPA on the emphasis placed on statistical significance.

Statistical Significance. Epidemiologic studies are most credible when the results are clear and precisely associate exposure and effect. Knowledge of a biological mechanism by which a substance can cause an effect increases credibility. Results that show dose-response relationships between more severe or more frequent disease and higher exposures are the most believable.

The requirement that epidemiologic results be statistically significant is of vital importance. Satisfaction of that requirement establishes a level of confidence, usually 95 percent, that study results did not occur by chance. Study results that are not statistically significant are deemed suspect and are not suitable grounds from which to conclude that cause-and-effect relationships exist.

In a 1991 report,*Environmental Epidemiology: Public Health and Hazardous Wastes*, the National Research Council, the research arm of the National Academy of Sciences, stated,

> Historically, discussions on causality have proceeded once a statistically significant relationship between a potential casual factor and a disease has been found. The requirement that a finding be statistically significant has been a convention of epidemiologic research. If results have a likelihood of only 5 percent or less of occurring by chance, then they are usually considered statistically significant, as measured by a number of customary tests. [32]

Thus, statistical significance is a traditional and standard tool used to rule out chance as the factor that has caused the observed results of an epidemiologic study.

Statistical significance is not an arcane idea; it pervades the medical literature. David Plotkin, a physician writing in the *Atlantic Monthly* about breast cancer, called statistical significance "the touchstone of medical research" and explained it to his readers: "'Significant,' an important term, means that statistical tests indicate the effect is probably not due to chance." [33] Marcia Angell, executive editor of the *New England Journal of Medicine*, states, "For a scientific finding to be accepted, it is customary to require a 95 percent probability that it is not due to chance alone." [34]

Statistical significance, by itself, is no guarantor of truth. Norman Breslow, a statistician at the University of Washington, warns that the calculation of significance takes into account only random variation in the data; it does not and cannot account for systematic errors in data collection and analysis. [35] And Sander Greenland, an epidemiologist at UCLA, goes further:

> What people want to do when they see a 95% confidence [interval] is say "I bet there's a 95% chance the true value is in there." Even if they deny it, you see them behaving and discussing their study result as though that's exactly what it means. There are certain conditions under which it's not far from the truth, but those conditions are generally not satisfied in an epidemiologic study. [36]

The importance of statistical significance in reducing the role of chance appears in an article written for a lay audience, in the comments of an editor of one of the world's leading medical journals, and in the professional comments of statisticians and epidemiologists. It is not sufficient, by itself, to guarantee the correct interpretation, but it is essential. The EPA may have good reasons for its decision to drop statistical significance as a criterion for an acceptable epidemiologic study, but it gives none. We cannot imagine what they might be.

Statistical significance has long been the Achilles heel of some risk assessors intent on "finding something" (and ensuring their success in obtaining research funding and other rewards) and of some regulators intent on expanding their authority. [37] Statistical significance has stood in the way of establishing relationships between elevated cancer

rates and such things as electromagnetic fields (EMF), dioxin, environmental tobacco smoke (ETS), dietary pesticide residues, and hazardous waste sites. The new guidelines answer the prayers of those whose dreams have been blocked by statistical significance.

The EPA learned its lesson about statistical significance twice when the agency did its cancer risk assessments for EMF and ETS in the early 1990s. Statistical significance proved such a barrier to associating EMF with cancer that the EPA's attempt to justify an EMF regulatory program imploded. Learning from that experience, the EPA altered statistical significance in its ETS risk assessment: it deviated from conventional scientific practice regarding statistical significance and lowered the confidence limit from 95 percent to 90 percent. That deviation allowed the EPA to claim "statistical significance" and conclude that ETS was associated with increased lung cancer risk. The scientific community heavily criticized the EPA for its ETS risk assessment. [38] The EPA's new attitude appears to be "why deal with criticism when you have the power to change the rules?"

Disappearance of Statistical Significance from the Draft Guidelines. According to the EPA's 1986 guidelines, three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association. [Confounding results when hidden factors contribute to a result. A common example is cigarette smoking, which confounds every study of relationships between alcohol and health effects because most drinkers smoke. Therefore, any apparent alcohol-health effect link might be caused by or influenced by smoking.]
3. The association is unlikely to be due to chance. [39]

The last criterion is "statistical significance."

> In contrast, the 1996 guidelines propose that
>
> a causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of the criteria is conclusive by itself, and the only criterion that is essential is the temporal relationship. . . .
>
> Temporal relationship: The development of cancers requires certain latency periods, and while latency periods vary, existence of such periods is generally acknowledged. Thus, the disease has to occur within a biologically reasonable time after initial exposure. This feature must be present if causality is to be considered.
>
> Consistency: Associations occur in several inde pendent studies of a similar exposure in dif ferent populations, or associations occur consistently for different subgroups in the same study. This feature usually constitutes strong evidence for a causal interpretation when the same bias or confounding is not also duplicated across studies.
>
> Magnitude of the association: A causal relation ship is more credible when the risk estimate is large and precise (narrow confidence in tervals).
>
> Biological gradient: The risk ratio (i.e., the ratio of the risk of disease or death among the exposed to the risk of the unexposed) increases with increasing exposure or dose. A strong dose response relationship across several categories of exposure, latency, and duration is supportive for causality given that confounding is unlikely to be correlated with exposure. The absence of a dose response relationship, however, is not by itself evidence against a causal relationship.
>
> Specificity of the association: The likelihood of a causal interpretation is increased if an exposure produces a specific effect (one or more tumor types also found in other studies) or if a given effect has a unique exposure.
>
> Biological plausibility: The association makes sense in terms of biological knowledge.

> Information is considered from animal toxicology, toxicokinetics, structure-activity relationship analysis, and short-term studies of the agent's influence on events in the carcinogenic process considered.
>
> Coherence: The cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the dis ease, i.e., the entire body of knowledge about the agent. [40]

Although the number of criteria has increased from three in the 1986 guidelines to seven in the proposed guidelines, one is conspicuous by its absence. Statistical significance is not to be found.

The EPA claims a distinguished pedigree for its criteria, stating that they "are modeled after those developed by [the English epidemiologist] Bradford Hill." In fact, the EPA's omission of statistical significance represents a jaundiced reading of Hill's 1965 paper. Hill wrote that his criteria should be applied to observations that

> reveal an association between two variables [an exposure and a health effect], perfectly clear-cut and beyond what we would care to *attribute to chance*. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation? [41]

Clearly, elimination of chance--a demonstration of statistical significance--is a threshold requirement that must be met before the other criteria are considered.

Was omission of statistical significance from the proposed guidelines a simple oversight? Not likely. In fact, the proposed guidelines contain in several places language that gives the misleading impression that statistical significance is included, but the section on "Criteria for Assessing Adequacy of Epidemiologic Studies" states,

> Statistical Considerations. The analysis applies appropriate statistical methods to ascertain whether or not there is any significant association between exposure and effects. A description of the method or methods should include the reasons for their selection. Statistical analyses of the potential effects of bias or confounding factors are part of addressing the significance of an association, or lack of one, and whether a study is able to detect any effect. [42]

That section mentions doing statistical analyses only to determine whether statistical significance exists. It does not require statistical significance as a condition for concluding that a causal relationship exists.

The new guidelines' section on "Weight of Evidence Evaluation for Potential Human Carcinogenicity" states,

> Human Evidence. Analyzing the contribution of evidence from a body of human data requires examining available studies and weighing them in the context of well-accepted criteria for causation.
>
> . . . A judgment is made about how closely they satisfy these criteria, individually and jointly, and how far they deviate from them. Existence of temporal relationships, consistent results in independent studies, strong association, reliable exposure data, presence of dose-related responses, freedom from biases and confounding factors, and high level of statistical significance are among the factors leading to increased confidence in a conclusion of causality. [43]

Although statistical significance is mentioned as a factor that increases confidence in a conclusion of causality, this language does not make statistical significance a basic requirement.

Table 2, which is taken from Figure 2-1 in the proposed guidelines, summarizes how the EPA intends to weigh data from human studies and to use statistical significance as one of several criteria that may be satisfied. [44]

Table 2
EPA's Factors for Weighing Human Evidence

Increase Weight	Decrease Weight

Number of independent studies with consistent results	Few studies Equally well designed and conducted studies with null results
Most causal criteria satisfied Temporal relationship Strong association Reliable exposure data Dose-response relationship Freedom from bias and confounding Biological plausibility High statistical significance	Few causal criteria satisfied
Source: Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," Federal Register 61 (April 23, 1996), Figure 2-1, p. 17982.	

Whereas Bradford Hill and the National Research Council set statistical significance as a threshold criterion, the EPA buried it at the end of a list of factors, and it is not essential. In fact, the table is consistent with the text of the proposed guidelines, which says that "high statistical significance" increases confidence in a conclusion of causality, but the absence of statistical significance per se does not hinder a conclusion of causality.

Animal Bioassays

Twenty years ago National Cancer Institute scientists published guidelines for testing chemicals for carcinogenicity in small laboratory animals. [45] The guidelines called for testing chemicals in two species of animals--almost always rats and mice--at two doses--one that is very close to a frankly toxic dose and another that is one-half or one-quarter the high dose--and exposing the animals for two years, which is roughly their expected life span. Throughout the test, a pathologist examines each animal that dies for macroscopic and microscopic tumors, and at the end of the test, each surviving animal is killed and examined for tumors. That basic outline for the bioassay is followed to this day, sometimes with a third dose level, one-quarter or one-eighth of the high dose, being added. The total number of animals required to test each suspect chemical ranges upward from a minimum of 600: 50 female and 50 male rats and 50 female and 50 male mice for each tested dose and for the zero-dose control group.

The National Cancer Institute guidelines did not describe anything like a complete test for carcinogenicity. Indeed, the test is a "screening assay" to detect whether the tested chemical is capable of causing cancer under conditions that favor tumor formation. In those long-ago days, it might have been assumed that the screening assay would be followed by molecular and biochemical experiments to pin down the mechanism of the chemical's effect and to understand how the animal response to the chemical at the tested dose was related to possible human effects. Such has not been the case. The screening test, often with no other information, has been pressed into service to identify substances that present a cancer hazard and to serve as the basis for various risk assessment models for estimating human cancer risk.

The tenet of toxicology that animal responses to chemical exposures are predictive of human responses is the basis of the EPA's assumption that a substance that causes cancer in test animals will cause cancer in humans. Few people would argue the opposite, but many scientists object to the EPA's routine reliance on results from high-dose animal experiments in making predictions about human risks at far lower exposures.

Armed with the results of animal tests and a computer program to estimate cancer risks, anyone can crank out cancer risk estimates, and the EPA has done so over the years. There are many objections to that mechanical process. The bioassay produces too little biological information, and the standard extrapolation model cannot capture the complexities of using results from highly exposed animals to predict risks in humans exposed to far smaller amounts. Allegedly, the EPA's proposed guidelines respond to some of those criticisms. In our opinion, they are a call for much more information with no indication that the additional information will produce more than cosmetic changes in the EPA's behavior.

Maximum Tolerated Dose. The high dose in animal tests is known as the maximum tolerated dose (MTD). It is usually selected by determining a dose just below the one that causes frank toxicity after a few weeks' to 90 days' exposure. As expected, continual, lifetime exposure often produces more toxicity during the two-year cancer test than was seen in the shorter test.

MTD is not well defined, but the draft guidelines say that it is

> a dose that produces some toxic effects without either unduly affecting mortality from effects other than cancer or producing significant adverse effects on the nutrition and health of the test animals. [46]

The MTD is at least marginally toxic, and what exactly "unduly" and "significant adverse" mean can become very important in disagreements about interpretation. In any case, the MTD-exposed animals are a little bit "sick" from exposure to the chemical throughout their lifetimes.

The other dose in a two-dose test or the third dose in a three-dose test is called the "low dose." That terminology is a terrible obfuscation. The dose may be "low" because it does not cause frank toxicity, but it is still no less than one-half or one-quarter of the dose that has a toxic effect. In all cases, the MTD and even the low dose are hundreds, thousands, tens of thousands, or hundreds of thousands of times higher than human environmental doses.

According to the proposed guidelines, "The default assumption is that effects seen at the highest dose tested are appropriate for assessment, but it is necessary that the experimental conditions be scrutinized." [47] Clearly, the default assumption imposes the burden of proof on those who object to the EPA's preferred interpretation that any evidence of carcinogenicity is acceptable regardless of other information. Even convincing data that show cancer was a secondary effect may be disregarded.

> If adequate data demonstrate that the effects are solely the result of excess toxicity rather than carcinogenicity of the tested agent per se, then the effects may be regarded as not appropriate to include in assessment of the potential for human carcinogenicity of the agent. [48]

The use of the default assumption coupled with the comment that "adequate data" that contradict it are not necessarily sufficient to move it aside characterizes the proposed guidelines, regardless of any EPA claims of flexibility.

Animal Cancers and Human Risks. What does an excess of cancers in the exposed animals mean? As one of its "default assumptions," the EPA interprets any increase in animal tumors as indicative of human hazard.

To be fair, the EPA has made at least one exception to that assumption, and it is moving toward making an exception for another tumor. [49] A continuation of that process would reduce the number of types of animal tumors that are taken as indicating human risk, but listing exceptions one by one promises to be a long process.

High Doses and Cancer Risks. Ames and Gold and others raise general and fundamental objections to the EPA's default position that animal tumors induced by high doses of chemicals predict human cancers. [50] High doses cause cell killing, which leads to cell multiplication to replace the killed cells. Cell multiplication requires DNA synthesis, and the mutational events that always accompany DNA synthesis can lead to tumors. Ames and his colleagues have tabulated information about animal cancer tests and determined that about 50 percent of all tested chemicals--whether natural or manufactured--cause tumors in test animals.

According to Ames and Gold, that high percentage is an artifact of the high doses. They recommend that the EPA abandon the use of the MTD. Many scientists share their misgivings about the MTD but are frustrated because they cannot devise a substitute for it. In 1993 a committee of the National Research Council said that results from MTD tests (essentially all cancer bioassays) should be interpreted with care, but the majority of the committee could not suggest an alternative to such tests. [51]

Three years later, another National Research Council committee moved closer to condemnation of dependence on the

high-dose animal bioassays:

> Laboratory studies have identified a much larger number [larger than the number identified through epidemiologic studies] of synthetic and naturally occurring agents capable of causing cancer in experimental animals. However, prediction of human cancer risks based on laboratory results is uncertain because extrapolations must be made from high to low doses and from animals to humans. Thus, important questions remain about the relevance of findings from animal studies for predicting human cancers. In particular, rodent carcinogens, some of which may act by increasing cell proliferation only at high doses, may pose little or no risk at low doses. [52]

Those comments summarize the general belief that the bioassays are flawed. Flawed or not, it is often claimed that the bioassay is the only available source of information about cancer risk and that the MTD is necessary to keep the tests of manageable size.

No substitute is needed for the tests or the MTD. Given the tiny effect of environmental carcinogens on cancer risk, the tests can be dropped with no expected effect on public health. However, until the policy decisions behind the unsupported belief that environmental chemicals are major risks are analyzed, no change can be expected in the EPA's approaches to environmental carcinogens.

If humans were ever exposed to an MTD, they would probably respond much as animals do. They would probably become at least a little bit ill; their appetites would be affected; their biochemical balances would be upset. It is even likely that humans exposed to the MTD would develop excess cancers. But humans are not exposed to such doses. What do results at high doses mean for risks at far lower exposures?

Risk Estimation Models

Opposing camps have battled over questions related to extrapolating from effects of the MTD to the expected risks at the far lower environmental exposure levels. At one end of the debate, Ames and his colleagues do not attempt such extrapolation, arguing that the high-dose effects have no value as predictors of effects at far lower doses. Near the other end, the EPA has consistently advocated and succeeded in implementing some form of "linear, no-threshold" risk model, which predicts high risks compared to most other models.

The underpinning of the linear, no-threshold models is the fact that mutations are involved in cancer. Mutations--changes in DNA--in genes that regulate cell growth and metabolism have been found in many cancers in both animals and humans, and they will probably be found in additional kinds of cancers as scientists identify the pertinent mutations.

Some carcinogens are mutagens--agents that cause mutations. Once a chemical interacts with DNA and causes a mutation, there is a finite probability that the mutation will be fixed in that cell, and when the cell divides, that the mutation will be passed on to both daughter cells. In a clone of tens, hundreds, or thousands of cells that arises from a single dividing cell that contains a mutation, every cell will have the mutation. If the mutation leads to cancerous growth, it is easy to imagine that one interaction between a mutagen and DNA could produce a cancer. (Most mutations have no such effect. Ames and Gold have shown that, on average, there are more than 100,000 mutations per rodent cell each day and about 10,000 mutations per human cell each day. [53] Clearly, most mutations are repaired or occur in locations where they cause no lasting deleterious effects.)

The mutagen-carcinogen connection is at the base of the theory that there is some probability that even one molecule of a mutagen can lead to cancer and that the probability of cancer directly increases with dose. To put it simply, the risk from 10 molecules is predicted to be 10 times the risk from a single molecule, and risk is predicted to increase "linearly" with dose.

In the late 1970s the EPA estimated cancer risks by plotting the number of tumor-bearing animals versus the dose and drawing a straight line from data points in the animal test to zero dose. From the line, the agency could estimate the risk for any dose between zero and the MTD. In the summer of 1980 the EPA adopted a more complicated "linear-ized

multistage" model. [54] The linearized multistage model really made very little difference in estimating risks because it preserved the linear relationship between dose and predicted effect at low exposure levels; it was incorporated into the EPA's 1986 guidelines and provided the agency's default positions for a decade.

The new proposed guidelines return to a modified straight-line method. [55] When all is said and done, however, the risks calculated by using the proposed model will not differ significantly from those calculated by using the linearized multistage model, which would not differ significantly from those calculated by using the original method. Despite the many words that have poured from the EPA, little has changed.

The EPA's Proposed "Nonlinear" Method for Determining Acceptable Exposures

A great schism separates those scientists and policy-makers who insist that linear, no-threshold models should be used to estimate risks posed by all carcinogens and those scientists and policymakers who insist that other models should be used for at least some carcinogens. The other models can be divided into two general kinds:

- Threshold models postulate that doses below a certain, critical level present no risk; risk arises only when the threshold dose is exceeded.
- Infralinear or sublinear or nonlinear models postulate that an S-shaped function relates dose to risk. At low doses, risk increases slowly. At doses above an inflection point, risks begin to increase more rapidly with dose.

The significant thing about both of those types of models is that they predict risks lower than those predicted with the linear model at environmental exposure levels.

The proposed guidelines outline a "default nonlinear model" as an alternative to the usual linear model. In the default nonlinear model, the lowest calculated dose of the chemical that is expected to increase the cancer rate by 10 percent (LED_{10}), is divided by environmental exposure levels to calculate a "margin of exposure" (MOE). For instance, if the LED_{10} were 1 mg and environmental exposures were 0.01 mg, the MOE would be 100. Risk managers can then consider whether the MOE is sufficiently high that no actions are needed or whether some steps are necessary to increase the MOE.

The MOE approach ignores the possibility that some exposures bear no risk at all. It is entirely possible that a given exposure (E) causes an adverse effect and that a lower exposure (E/10) does not. If that were the case, an animal test would show that E caused cancer and E/2 might not. Those data might convince the EPA that there was a nonlinear response to E, and the agency might elect to use its MOE method for estimating risks. On the basis of the finding that E caused cancer, the EPA would calculate a theoretical exposure that might cause a 10 percent increase in cancer and then decide on an MOE. That approach eliminates any consideration of a threshold exposure, or dose, below which there is no risk.

We Don't Know What Will Come from the MOE Approach

Recent analyses have shown that the bioassay and line-arized multistage model produce a quantitatively predictable result that can be estimated in 96 percent of tested cases by simple arithmetic. David Gaylor, a statistician at the Food and Drug Administration's National Center for Toxicological Research, and Lois Gold, a frequent collaborator with Bruce Ames, have analyzed the relationships between the MTDs of chemicals tested in bioassays and virtually safe doses (VSDs). (A virtually safe dose is the dose calculated to increase cancer risks by one in a million). MTDs vary greatly, differing by factors of up to 10,000 and more--the most toxic chemical causes toxic effects at doses 10,000 times lower than those required for the least toxic chemicals to cause adverse effects. Despite that great range of MTDs, Gaylor and Gold found, by examining the relationships between experimentally determined MTDs and VSDs, that dividing the MTD by 740,000 predicted the VSD for 96 percent of the carcinogens. [56] Determining an MTD does not tell us whether a substance will be a carcinogen when tested in a bioassay, but it does predict the VSD if the substance is carcinogenic.

If reliable tests could be developed to predict which substances can cause human cancer at environmental exposure levels, a combination of those tests with determination of the MTD could replace the costly and, in some cases,

misleading bioassay. Such tests can probably be developed only through detailed research on biochemical and molecular biological mechanisms, and spending money on the bioassay and other routine tests simply siphons off resources from research that might produce those tests.

The Gaylor and Gold result makes it possible to compare the outcomes of using the linear model with the possible results of using the EPA's MOE method. The comparison requires that we make an assumption about the dose of a carcinogen that will correspond to the EPA's LED_{10}(a lower bound on the dose associated with a 10 percent increase in cancer), and for the purposes of illustration, let us assume that a dose of 1/5 the MTD (MTD/5) is the LED_{10}. [57]

First, we consider two linear models for estimating cancer risks. According to Gaylor and Gold, the linearized multistage model will produce a VSD of MTD/740,000. The EPA's straight-line method, which is included in the proposed guidelines, will produce a VSD of MTD/500,000 (assuming that MTD/5 is the LED_{10}). [58] The choice between the two models makes little difference in the predicted risk; VSDs of MTD/740,000 and MTD/500,000 are essentially identical.

Now, let us consider the MOE approach. The EPA briefly describes five "factors" that the risk manager should consider in deciding on the magnitude of the MOE. Two of those factors have been used for years in the traditional threshold approach for setting limits to exposures to noncarcinogenic toxic substances. In that approach, the highest dose of a chemical that does not cause an adverse effect in humans or test animals is divided by a "safety factor" to set an acceptable exposure level.

To illustrate, let us assume that a daily dose of 10 mg of chemical C per kg of body weight in rats (10 mg/kg-d) affected the functioning of the nervous system and that a dose of 5 mg/kg-d had no effect. The no-observed-effect level of 5 mg/kg-d is then used with safety factors to set an upper limit for acceptable human exposures. Generally, two safety factors are multiplied together when animal toxicity data are available. A safety factor of 10 is used to allow for the possibility that the average human is 10 times more sensitive than rats to chemical C and an additional factor of 10 is used to allow for the possibility that the most sensitive human is 10 times more sensitive than the average human. The total safety factor is then 100, and based on the no-observed-effect level of 5 mg/kg-d, the acceptable human exposure level would be 5 mg/kg-d divided by 100, or 0.05 mg/kg-d. (In the unusual cases for which human data are available, a safety factor of 10 is used to allow for some people being 10 times more sensitive than the people involved in the study.)

The EPA states that LED_{10} will be the starting point for use of the MOE, and for purposes of illustration, let us assume again that LED_{10} is equivalent to MTD/5. The choice of MOE has a profound impact on the estimated risk.

If MTD/5 is associated with LED_{10}, and the risk manager decides to use the conventional safety factor of 100 as the MOE, the acceptable level of exposure will be MTD/5 divided by 100, or MTD/500. In fact, a higher safety factor would be used because LED_{10} is a calculated effect level, not a measured no-effect level, and the MOE would probably be increased by another factor of 10 to a total of 1000. That would produce an acceptable exposure of MTD/5000, and it would greatly lighten the regulatory burden because the acceptable exposure level of MTD/5000 would be 100 times higher than the VSD. (Additional factors could be multiplied into the MOE to produce still lower acceptable doses; see Table 3).

There will probably be a strong inclination for risk managers to choose MOEs of 10,000 or more. They will be aware that under the old guidelines risks for all carcinogens would have been estimated using the linearized multistage model, with the VSD being about MTD/740,000. In the interest of "prudence," most managers can be expected to select MOEs that will bring the acceptable exposures nearer to MTD/740,000 rather than leave them near MTD/5000.

Table 3
Virtually Safe Doses and Acceptable Exposures Using the EPA's MOE Method

	Acceptable Exposure

VSDs Associated with a One-in-a-Million Increase in Cancer Risk		Using EPA's Proposed "Nonlinear" MOE Method[a]	
Method of Estimation	VSD	Chosen MOE	Acceptable Exposure
Gaylor and Gold's approximation of the linearized multistage model	MTD/740,000	100 1000 10,000 100,000	MTD/500 MTD/5000 MTD/50,000 MTD/500,000
EPA's proposed straight-line method[a]	MTD/500,000		
[a]Assuming MTD/5 = LED10.			

Regulators will have a more compelling reason for selecting a large MOE. Few, if any, carcinogens are present in the environment at levels as high as MTD/5000. Unless the MOE is set large enough to justify reducing exposures to less than MTD/5000, there will be no need for the EPA. That simple relationship will not go unnoticed.

Perhaps All Toxic Effects Have Thresholds

In marked contrast to the EPA's attachment to linear models, James D. Wilson of Resources for the Future (a Washington think tank) has proposed that a threshold model be used for estimating all risks from environmental chemi-

cals. [59] He argues that there is no scientific justification for the no-threshold model, even for mutagenic carcinogens. The major reason for its continued use, he says, is that it makes certain policy decisions automatic, relieving the policymaker from having to weigh competing values in deciding on an acceptable exposure level. The big loser in this process, besides the manufacturer or user who has to reduce exposures more than is necessary (and, in the extreme, discontinue manufacture or use), is science. Science loses because the dogma that supports the no-threshold policy is based on old findings and old analyses. Obsolete as it is, that dogma weakens the importance of science in what should be the technical part of risk assessment--estimating risks.

Tests for Biological Effects Other Than Tumors

Progression from a normal cell to a cancer cell involves several (the number is unknown) biochemical steps. Great hopes have been pinned on the development of tests that can detect those biochemical steps. Those tests could, when sufficiently validated, provide a measure of the carcinogenic potency of chemicals that would be quicker, more precise, and less expensive than the standard bioassay that requires hundreds of animals, years to complete, and high-dose exposures. Moreover, such tests could provide information about the mechanism by which a substance causes cancer in a test animal. Some such tests are now available, and the EPA expects to make use of them in deciding when to use a linear or a nonlinear risk assessment model.

The EPA says the linear model will be used "when the mode of action information is supportive of linearity or, alternatively, is insufficient to support a nonlinear mode of action." The hurdle for choosing the MOE approach is higher:

> When adequate data on mode of action show that linearity is not the most reasonable working judgment *and* provide sufficient evidence to support a nonlinear mode of action, the default changes to a different approach--a margin of exposure analysis--which assumes that nonlinearity is more reasonable. [60]

The EPA does not define "mode of action," and it provides no suggestion about how it interprets "adequate" or "sufficient" or "supportive." In practice, the EPA will probably consider information about the mutagenic activity of a chemical in deciding about mode of action. Almost every other country in the world makes that distinction and uses a

linear model for estimating risks for mutagenic carcinogens and threshold models (not MOE procedures), which predict far lower risks, for estimating risks of nonmutagenic carcinogens. The proposed guidelines, however, do not indicate the weight that will be given to results from mutagenicity tests.

Most of the tests mentioned in the proposed guidelines are still in the research and development rather than application phase, and their exact uses are not yet known. In any case, to a greater or lesser degree, every such test will present a new extrapolation problem. For instance, let us assume a specific change in DNA is associated with a particular cancer and that the chemical being investigated causes that change. What is the relationship between dose and frequency of the change? What is the relationship between frequency of the change and frequency of cancers? What other biochemical events must occur in conjunction with the DNA change to result in cancer? Does the chemical influence the frequency of the other biochemical events on the pathway to cancer? Are all those relationships the same in the test system and in humans? Each of those questions and many others will have to be answered. None is likely to be easy.

It is, however, easy to predict the ramifications of the introduction of those new tests. The EPA is likely to embrace results from unproved tests that support conclusions that a chemical is a carcinogen. Indeed, in response to a direct question, EPA officials acknowledged that, on the basis of such tests, the agency could carry out a cancer risk assessment on a chemical that had not been shown to be associated with cancer in animal tests or human studies. [61] Conversely, industry will herald the results of tests that indicate that biochemical changes that preceded cancer at high doses are not seen at low doses. As it does in all cases, however, the EPA reserves the power to choose which data to accept, with what are surely predictable outcomes.

Conclusions

The proposed changes in interpretation of epidemiologic studies and animal tests will have different effects. The EPA's dropping any requirement for statistical significance may open the door to the classification of many more substances as human carcinogens. It will likely lead to regulation of more chemicals, with the associated costs, that will have no effect on human health. The results of the proposed changes in interpretation of animal tests are difficult to project, but they will probably make little difference.

Statistical Significance Should Be Required Along with Other Rigorous Tests of Epidemiologic Results

The EPA's plans to drop statistical significance as a criterion for evaluation of epidemiologic studies mean that risk assessors may have to consider study results that are almost certainly the product of chance and that the public will be inundated with reports of effects that are not real. The EPA's plans are a regulator's dream come true. Without the requirement for statistical significance, the regulator will be able to pick through all the available studies of a particular chemical, select the ones that support his desired conclusion, and include them as evidence, whether or not the results mean anything.

The EPA's backing away from the requirement for statistical significance is especially difficult to fathom, given the statements of leading statisticians and epidemiologists that statistical significance is a primary safeguard against the drawing of erroneous conclusions. The epidemiologists favor more rigorous examination of studies and more stringent safeguards against false positive results "to avoid causal inferences on the basis of isolated studies or even groups of studies in the absence of compelling biomedical evidence." [62]

Billions of dollars in regulatory costs hang in the balance when the EPA evaluates epidemiologic findings. Surely Congress and the public should expect the agency to apply the same criteria to those evaluations as do scientists and scientific journals.

Considering a New, Noncancer, Scare in the Absence of Statistical Significance

Since the 1960s and 1970s, fear of cancer has been an important device with which the EPA and the extremist parts of the public health and environmental communities have commanded the public's attention. Despite the claims, the much ballyhooed cancer epidemic has not come to pass. With weekly and almost comical press reports of studies that associate everything from abortions, the lack of breastfeeding, or vitamin A with increased cancer risk, the public has

become increasingly skeptical about and even immune to the cancer scare. Society was surely fortunate that statistical significance stood in the way of the fearmongers' attempts to use epidemiology to bolster the cancer scare.

Despite the abject failure of the cancer scare, other scares have been trotted out over the years. The newest scare is environmental endocrine disrupters, or environmental estrogens. It has been theorized, most recently in *Our Stolen Future*, that man-made chemicals in the environment are interfering with our normal hormonal functions and thereby causing, not only cancer, but infertility, lower sperm counts, birth defects, and decreased intelligence and survival. [63] Whether man-made substances have any effect at all against the large background of estrogenic compounds that exist in nature is unclear, but Congress has already appropriated money for targeted research on the man-made compounds. [64]

If the EPA is successful in doing away with statistical significance as a criterion for epidemiologic studies, there is every reason to believe that the agency would drop that criterion in considering epidemiologic studies about environmental estrogens. In time, the environmental estrogen scare, like the cancer scare and other scares before it, will probably pass. However, we may face a future in which there is no barrier of statistical significance between unsubstantiated claims and government regulation. The additional regulations may actually harm public health by increasing the cost of fresh fruits and vegetables.

The EPA's Nonlinear Method for Estimating Cancer Risks Is Not Nonlinear

The EPA calls its MOE approach "nonlinear." It is not. It embodies a linear, no-threshold approach. It does not allow for a safe level of exposure. It says that somehow society (more specifically, regulators) will be able to decide that some fraction of an exposure level that causes an adverse effect is acceptable, and built into that approach is the idea that risk is reduced but never eliminated.

The EPA's Behavior Will Be More Important Than Guidelines

The 1986 guidelines acknowledged that risk models other than the linear one might be appropriate under certain conditions and indicated that the EPA would consider applying them if presented with sufficient evidence to support their use. That is an example of the EPA's stating a default position and a willingness to diverge from it. It appears to be an example of regulatory flexibility. All of society stands to gain from such flexibility. If a manufacturer produces data that convince the EPA not to estimate risks with a linear, no-threshold model, the manufacturer gains because he has to install fewer devices to control exposures and can avoid increasing prices to cover pollution control costs, and consumers gain from continued access, at lower cost, to the product.

How well have the 1986 guidelines worked? How often has the EPA deviated from its default position of using a straight-line extrapolation model? It depends on whom you ask. On the same day, at the same meeting, Richard Hill of the EPA said that the office that makes decisions about the risks from pesticides "not uncommonly deviates from linearity," and Dennis Paustenbach of the McLaren/Hart consulting firm stated that companies with major investments in toxicology and risk assessment programs had closed their laboratories because of the futility of trying to move the EPA from adherence to its default positions. [65] The evidence from actual industry behavior weighs more heavily than do the EPA's claims.

Whatever models are proposed for estimating cancer risks, the EPA reserves to itself the authority to decide if there is sufficient information to move away from the default linear model. That is hardly different from the 1986 guidelines, if it is different at all, and it preserves the capacity of the agency to say, "Yes, what you show us is interesting, but it's not quite sufficient to convince us that the default linear model is not the correct one."

Recommendations for the EPA

We make four specific recommendations for revising the proposed guidelines:

1. Restore statistical significance as the threshold criterion for determining whether epidemiologic evidence will be considered convincing.

2. Replace the vague references to "mode of action" as the determinant of whether to use the default linear or MOE risk estimation procedure with a statement that risks for mutagenic carcinogens will be estimated with a linear model and risks for all other carcinogens will be estimated with an MOE procedure. That will bring U.S. practice in line with that of European countries.
3. Explicitly state how the EPA will decide upon acceptable MOE levels. That is more a policy than a technical decision, and it needs public airing.
4. Decisions about whether epidemiologic data are convincing evidence that a chemical is a human carcinogen and about whether to use the default linear or MOE risk estimation procedure should be made reviewable by the EPA's Science Advisory Board upon the request of any interested party.

Recommendations for Congress

Most fundamentally, questions must be asked about continuation of any federal activities directed against alleged environmental carcinogens when there is little reason to expect them to make a difference to public health. Such questions require that Congress reopen discussion of what can be expected from the EPA's potential regulation of environmental carcinogens. As argued in this paper, the answer is "not much." It is possible that the correct answer is "nothing" or even "negative effects." If Congress considers those possibilities, the whole question of guidelines will be placed in a different context, namely, "What is the point of guidelines if they will have no discernible effect, and perhaps no effect at all, on public health?"

After reviewing the record of animal tests for predicting human cancer risks, the late Aaron Wildavsky, who wrote extensively about risk, concluded that they are an invalid method. [66] Like Ames and Gold and many others, he discounted the usefulness of the tests, and like Wilson and others, he found the EPA's risk assessment methods without foundation. Wildavsky moved from that conclusion to recommending that society throw out the tests (and, we add, the risk assessments that accompany them), accept evidence from epidemiology, and invest in research to understand the mechanisms by which environmental agents might cause cancer.

The evidence from epidemiology is straightforward: any harm from environmental carcinogens is so small as to be undetectable, and studies of the effects of far higher occupational exposures provide far better information about possible human risks than do animal tests. If epidemiologic evidence were considered, many fewer chemicals would be the targets of environmental regulatory crusades. Perhaps none would be. The reduction in such crusades will have absolutely no discernible effect on measured health outcomes because the harms from environmental exposures, if there are any, are undetectable.

Only Congress can make certain that serious effort is devoted to understanding the effects of environmental chemicals on cancer rates and to understanding the expected effects of the EPA's regulatory programs. That effort--the antithesis of the incremental, pecking-around-the-edges changes in risk assessment procedures that characterize the EPA's proposed guidelines--is necessary to effect any meaningful change in an expensive regulatory program that produces few benefits and that may be detrimental to public health because it increases the costs and limits the availability of fresh fruits and vegetables.

Notes

[1]. Bruce N. Ames and Lois Swirsky Gold, "The Causes and Prevention of Cancer: The Role of Environment," in The True State of the Planet, ed. Ronald Bailey (New York: Free Press, 1995), pp. 141-75; and Bruce N. Ames, Lois Swirsky Gold, and Walter C. Willett, "The Causes and Prevention of Cancer," Proceedings of the National Academy of Sciences 92 (1995): 5258-65.

[2]. Bruce N. Ames, Lois Swirsky Gold, and Mark K. Shigenaga, "Cancer Prevention, Rodent High-Dose Cancer Tests, and Risk Assessment," Risk Analysis (in press).

[3]. See Office of Technology Assessment, Assessment of Technologies for Determining Cancer Risks from the Environment (Washington: Government Printing Office, 1981), pp. 124-27; Dennis J. Paustenbach, "A Survey of

Health Risk Assessment," in The Risk Assessment of Environmental Hazards, ed. Dennis J. Paustenbach (New York: Wiley-Interscience, 1988),

pp. 27-124; Bruce N. Ames and Lois Swirsky Gold, "Chemical Carcinogenesis: Too Many Rodent Carcinogens," Proceedings of the National Academy of Sciences 87 (1990): 7772-76; Samual M. Cohen and Leon B. Ellwein, "Risk Assessment Based on High-Dose Animal Exposure Experiments," Chemical Research in Toxicology 5 (1992): 742-48; and Office of Technology Assessment, Researching Health Risks (Washington: Government Printing Office, 1993), pp. 120-25.

[4]. Environmental Protection Agency, "Guidelines for Carcinogenic Risk Assessment," Federal Register 51 (September 24, 1986) 33992-34117.

[5]. Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," Federal Register 61 (April 23, 1996): 17960-18011. Republished in full in Chemical Regulation Reporter 20, no. 3 (April 19, 1996):

73-122.

[6]. "Cancer and Environment: Higginson Speaks Out," Science 205 (September 28, 1979): 1363.

[7]. Ibid., pp. 1363-64.

[8]. Richard Doll and Richard Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," Journal of the National Cancer Institute 66 (1981): 1193-1308.

[9]. Larry Kessler, a statistician at the Food and Drug Administration, appeared on the August 20, 1996, broadcast of NBC's Dateline. He stated that "the greatest single risk is aging."

[10]. Susan S. Devesa et al., "Recent Cancer Trends in the United States," Journal of the National Cancer Institute 87 (1995): 175-82.

[11]. Ibid., p. 175.

[12]. Ibid., p. 181.

[13]. Philip Cole and Warren Sateren, "The Evolving Picture of Cancer in America," Journal of the National Cancer Institute 87 (1995): 159-60.

[14]. Environmental Protection Agency, Unfinished Business: A Comparative Assessment of Environmental Problems, Appendix I to Report of the Cancer Risk Work Group (Washington: EPA, February 1987).

[15]. Michael Gough, "Estimating Cancer Mortality: Epidemiological and Toxicological Methods Produce Similar Assessments," Environmental Science and Technology 23 (1989):

925-30.

[16]. Michael Gough, "How Much Cancer Can EPA Regulate Away?" Risk Analysis 10 (1990): 1-6.

[17]. Werner K. Lutz and Josef Schlatter, "Chemical Carcinogens and Overnutrition in Diet-Related Cancer," Carcinogenesis 13 (1992): 2211-16.

[18]. National Research Council, Carcinogens and Anticarcinogens in the Human Diet (Washington: National Academy Press, 1996), pp. 336-37.

[19]. Ames and Gold, "The Causes and Prevention of Cancer: The Role of Environment"; National Research Council, Carcinogens and Anticarcinogens in the Human Diet; and Walter C.

Willett, "Diet, Nutrition, and Avoidable Cancer," Environmental Health Perspectives 103, supplement 8 (1995): 165-70.

[20]. Michael Gough, "It's Not Science: What Can Science Do about It?" Health Physics 71 (1996): 275-78.

[21]. See, for example, Karl Popper, Popper Selections, ed. David Miller (Princeton, N.J.: Princeton University Press, 1985), pp. 133-206.

[22]. Paul Davies, The Mind of God: The Scientific Basis for a Rational World (New York: Simon and Schuster, 1992), p. 28.

[23]. Some people object to this statement, saying, for instance, that exposures to vinyl chloride cause a form of liver tumor that is so rare that it is a hallmark of exposure. True enough, but no one has ever convincingly shown that exposure to vinyl chloride outside the workplace has caused the disease. In any case, there may be some exceptions to our statement. We would like to know about them.

[24]. Katherine Kelly, "In Search of 'Zero Risk,'" Wall Street Journal, February 24, 1995, editorial page.

[25]. Let us assume that there are 240 million people in the United States, that each person's lifetime cancer risk is increased by one in a million by the assessed exposure, and that the average life span is 70 years. The predicted number of cancer cases each year is then 240,000,000 people/1,000,000 person-lifetimes x 1 lifetime/70 years = ca. 3 cases/year.

[26]. Steven Milloy, Science without Sense (Washington: Cato Institute, 1995).

[27]. Tammy O. Tengs et al., "Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness," Risk Analysis 15 (1995): 369-90.

[28]. Tengs et al. reported the following regulatory costs for life-year saved, ranked by regulatory agency: Federal Aviation Administration, $23,000; Consumer Product Safety Commission, $68,000; National Highway Safety Administration, $78,000; Occupational Safety and Health Administration, $88,000; EPA, $7,600,000.

[29]. Jeanette Wiltse and Richard Hill of the Environmental Protection Agency, Comments at "Forum on Cancer Risk Assessment Guidelines," sponsored by the ILSI Risk Science Institute, Resources for the Future, and the Environmental Protection Agency, May 6, 1996, Washington.

[30]. Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," p. 17961.

[31]. Gary Taubes, "Epidemiology Faces Its Limits," Science 269 (July 14, 1995): 164-69.

[32]. National Research Council, Environmental Epidemiology: Public Health and Hazardous Wastes (Washington: National Academy Press, 1991).

[33]. David Plotkin, "Good News and Bad News about Breast Cancer, Atlantic Monthly, June 1996, pp. 68-69.

[34]. Marcia Angell, Science on Trial (New York: W. W. Norton, 1996), p. 114.

[35]. Quoted in Taubes, p. 168.

[36]. Quoted in ibid.

[37]. See, generally, Milloy.

[38]. See C. Stephen Redhead and Richard E. Rowberg, "Environmental Tobacco Smoke and Lung Cancer Risk," Congressional Research Service, 1995, photocopy.

[39]. Environmental Protection Agency, "Guidelines for Carcinogenic Risk Assessment," p. 33999. Emphasis added.

[40]. Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," p. 17974.

[41]. A. Bradford Hill, "The Environment and Disease: Association or Causation?" Proceedings of the Royal Society of Medicine, Occupational Medicine 58 (1965): 295. Emphasis added.

[42]. Environmental Protection Agency, "Proposed Guidelines for Carcinogen Risk Assessment," p. 17974.

[43]. Ibid., p. 17981.

[44]. Ibid., p. 17982.

[45]. James M. Sontag, Norbert P. Page, and Umberto Saffiotti, Bioassay in Small Rodents (Bethesda, Md.: National Cancer Institute, 1976).

[46]. Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," p. 17975.

[47]. Ibid., p. 17967.

[48]. Ibid. Emphasis added.

[49]. The exception to that generalization (mentioned repeatedly in the proposed guidelines) is leaded-gasoline-caused kidney tumors in male rats. Such gasoline does not cause kidney tumors in female rats or in mice of either sex. The biological reason for that difference is known: the enzyme necessary for tumor formation is at much lower levels in the other animals than it is in male rats; it is also at much lower levels in humans. As a result, the EPA does not consider male rat tumors that arise through that biochemical process predictive of human risk.

Richard Hill of the EPA said that EPA staff have prepared a report for the EPA Science Advisory Board that says that certain pesticide-caused thyroid tumors are not expected to occur at human exposure levels and recommends that such tumors not be considered as evidence of human risks. He made his remarks at the "Forum on Cancer Risk Assessment Guidelines."

[50]. Bruce N. Ames and Lois S. Gold, "Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis," Science 249 (August 31, 1990): 970-71; Lois Gold et al., "Possible Carcinogenic Hazards from Natural and Synthetic Chemicals," in Setting Priorities in Comparative Environmental Risk Assessment, ed. C. R. Cothern (Boca Raton, Fla.: Lewis, 1993); and Ames, Gold, and Willett.

[51]. National Research Council, Issues in Risk Assessment: Use of the Maximum Tolerated Dose in Animal Bioassays for Carcinogenicity (Washington: National Academy Press, 1993).

[52]. National Research Council, Carcinogens and Anticarcinogens in the Human Diet, pp. 303-4.

[53]. B. N. Ames and L. S. Gold, "Endogenous Mutagens and the Causes of Aging and Cancer," Mutation Research 250 (1991): 3-16.

[54]. Office of Technology Assessment, Technologies for Determining Cancer Risks from the Environment (Washington: Government Printing Office, 1981), p. 162.

[55]. The original straight-line method started the extrapolation from an actual data point in the animal experiment. In contrast, the proposed method starts from the calculated "lower 95 percent limit" on the dose that is associated with a 10 percent increase in tumors. (In different words, the dose of the substance that would cause a 10 percent increase in tumors is estimated from the experimental data and then a statistical method is used to calculate the lowest dose that might cause the 10 percent increase.) The use of the "lowest effect dose" that causes a 10 percent increase in tumors (LED10) increases the estimated risk as compared to the risk estimated on the basis of the dose that was observed to be associated with the 10 percent increase in tumors.

[56]. David W. Gaylor and Lois S. Gold, "Quick Estimate of the Regulatory Virtually Safe Dose Based on the Maximum Tolerated Dose for Rodent Bioassays," Regulatory Toxicology and Pharmacology 22 (1995): 57-63.

[57]. In fact, the possible range for the dose is quite small. It cannot be greater than MTD, and it is never much smaller than MTD/10. In any case, whether it is MTD, MTD/5, MTD/10, or some value in between makes little difference because the other values in the calculation vary much more.

[58]. Dividing both LED10 and MTD/5 by 100,000 results in the LED for a one-in-a-million risk being equivalent to

MTD/500,000.

[59]. James D. Wilson, "Thresholds for Carcinogens: A Review of the Relevant Science and Its Implications for Regulatory Policy," Resources for the Future, Washington, 1996.

[60]. Environmental Protection Agency, "EPA Proposed Guidelines for Carcinogen Risk Assessment," p. 17969. Emphasis added.

[61]. Thomas Starr of the Environ Corporation asked the question at the "Forum on Cancer Risk Assessment Guidelines."

[62]. Dimitrios Trichopoulos, Harvard University, quoted in Taubes, p. 164.

[63]. Theo Colborn, Dianee Dumanoski, and John Peterson Myers, Our Stolen Future (New York: Dutton, 1996).

[64]. On the effects of man-made substances, see Jonathan Tolman, Nature's Hormone Factory: Endocrine Disrupters in the Natural Environment (Washington: Competitive Enterprise Institute, March 1996).

[65]. Richard Hill and Dennis Paustenbach, Comments at "Forum on Cancer Risk Assessment Guidelines."

[66]. Aaron Wildavsky, "Regulation of Carcinogens: Are Animal Tests a Firm Foundation?" Independent Review 1 (1996): 29-54.