Letters

Estimating the Greenhouse Effect

In October, the U.S. Environmental Protection Agency (EPA) issued a report entitled "Can we delay a greenhouse warming?" The report was widely interpreted as answering that question essentially in the negative. In the words of Philip Shabecoff of the *New York Times* (*1*): "[The] warming trend, the result of a buildup of carbon dioxide in the atmosphere, is both imminent and inevitable." And "no strategy . . . even a total ban on the use of fossil fuels, could do more than delay the warming effect a few years."

A careful reader of the EPA report will recognize the need for some important qualifications to such statements. First, most students of the CO_2 issue would agree, I think, that some warming is probably unavoidable, perhaps an increase of 1° or 2°C in global annual average temperature, depending in part on the still-uncertain sensitivity of climate change to increasing atmospheric CO_2. But much higher temperature increases, like 5° to 10°C, which could conceivably result from full exploitation of the world's recoverable resources of fossil fuels, are by no means unavoidable. Although an immediate, total ban on fossil fuels (not exactly the case considered by EPA, but close to it) is entirely unrealistic, some future modification in the use of fossil fuels, in order to limit CO_2, might well be a practical possibility.

Second, the limited effect of large reductions in assumed future use of fossil fuels on the time when the calculated global temperature rise would reach 2°C, as presented by EPA, resulted in part from a large contribution to the calculated warming by infrared-absorbing gases other than CO_2, for example, methane, nitrous oxide, and chlorofluoromethanes. Their ever-increasing contributions to the warming were held fixed as functions of time, while the CO_2 contribution from fossil fuels was markedly reduced. In low-CO_2 scenarios, the other "greenhouse" gases contributed up to 80 percent of the calculated temperature rise.

It is generally recognized that the other greenhouse gases may be important; but neither their future sources and atmospheric concentrations nor their effect on climate can be estimated at all accurately at present. The EPA calculations may or may not prove to be correct. The implicit assumption that future sources and concentrations of the other greenhouse gases could not be controlled is probably incorrect.

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Reference

1. P. Shabecoff, *New York Times*, 18 October 1983, p. A1.

Cancer Prevention: Setting Priorities

The article "Cost-effective priorities for cancer prevention" by Milton C. Weinstein (1 July, p. 17) may offer a significant and potentially useful approach to the complex issue of setting research priorities for the prevention of human cancer. Weinstein's approach, however, appears to overlook a fundamental cost that may have a major impact on his cost-effectiveness analysis. Specifically, the cost of the total background of research that is necessary before any chemical is seen as an important candidate for rodent bioassay testing is likely to be less by several orders of magnitude than the cost of research needed to identify and justify any anticarcinogen as a legitimate candidate for human trials. For example, strongly positive responses for a new industrial chemical in one or more short-term screening tests may be sufficient justification to warrant rodent bioassay testing and subsequent governmental action. These data can be obtained for a total cost that certainly should not exceed the cost of the rodent bioassay itself.

By contrast, inhibitors of experimental chemical carcinogenesis can become legitimate candidates for human study only after exhaustive animal studies to determine species, organ, and carcinogen specificity; potency; toxicity; and most important, mechanism of action. Thus, to the estimated $4 million cost of the human trials of β-carotene should be added the cost of all the relevant worldwide human and animal experimentation that preceded and contributed to its recognition as a legitimate candidate for human anticancer trials. Although estimates of this cost are difficult to arrive at, one may suspect that they greatly exceed the $4 million cost of the actual human trials for anticarcinogenicity that Weinstein uses as his basic cost estimate. For example, a computer search of the Medline database reveals approximately 5700 articles relating to vitamin A dating back through 1966, with more than 10 percent of these relating directly to cancer research. If one estimates approximately $30,000 of research funds expended per publication, this represents an actual recent cost of 18×10^6 to 170×10^6, covering expenditures over only the past 17 years, to gather the data essential to identify retinoids as safe and potentially effective candidates for human trials. As Weinstein recognizes, β-carotene may represent a current best case for his arguments. The model will, of course, lack general validity if it applies to only a few such special cases. More recently recognized candidates as potential inhibitors, such as indole-3-carbinol and other plant phenolics, must undergo similar extensive, and costly, prior basic research if they are to prove fit for human trials. When such large factors are included as part of the real costs that must precede human trials, the cost-effective attractiveness of this approach over rodent bioassays cannot be as great as that estimated by Weinstein and, in fact, may disappear.

Weinstein has raised a very important issue. It is imperative, however, that administrative decisions on allocation of scarce research funds should not be based on cost-effectiveness models until these models are thoroughly scrutinized.

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Weinstein's approach to priority-setting for cancer research uses examples that are clearly not comparable. The results from extensive preliminary testing in both animals and humans must provide persuasive evidence of the value and safety of any proposed dietary intervention trial. Thus, the $4 million cited

for the clinical trial examining the relationship between β-carotene and cancer reduction significantly underestimates the actual costs of such research.

On the other hand, the $500,000 estimate of the cost of the bioassay of *p*-dichlorobenzene is a fairly close approximation of the actual cost of determining its carcinogenic potential in animals and informing society as to its possible hazard to humans. The characteristics of chemical carcinogenesis in animals and in humans appear to be identical, even though a single chemical may produce different cancers in different species. Animal experiments yield data that can be used to better predict or hypothesize actual human experience from exposure to the same chemical. Often animal data showing a carcinogenic response to a chemical precede human case reports or epidemiologic findings. For instance, Tomatis (*1*) identified seven such chemicals—aflatoxin, 4-aminobiphenyl, bis-(chloromethyl)ether, diethylstilbestrol, melphalan, mustard gas, and vinyl chloride; had these advance warnings been heeded, appropriate protective measures might have been initiated sooner.

Cost-effectiveness comparisons are also unfounded because the number of chemicals which are suitable for intervention trials similar to that undertaken on β-carotene is very limited, whereas the chemicals to which humans are exposed in the workplace or the environment, or both, number well into the thousands. Weinstein notes that β-carotene is "one of relatively few dietary factors that are now ready for prospective study."

In animal toxicity and carcinogenesis studies it is necessary to test those chemicals that are of importance on the basis of exposure or structure-activity relationships, or both, in order to develop a sufficient database to set priorities for testing other representatives from the multitude of untested chemicals and to develop reliable estimates of carcinogenic potency.

The cost-effectiveness of a dietary intervention trial that yields negative results may be questioned. However, both positive and negative animal cancer studies are cost-efficient because they provide important data on the factors that contribute to carcinogenic potential of environmental chemicals. Negative studies provide the public with some degree of confidence that certain chemicals are not toxic, while both positive and negative results are helpful in developing guidelines for the use of and exposure to numerous commercial chemicals.

Therefore, it is inappropriate to make comparisons between human intervention experiments and research aimed at identifying potentially toxic chemicals in the environment.

Weinstein estimates that dietary intervention with β-carotene will lead to 32 percent fewer lung cancer deaths annually, as well as diminutions of 35, 50, 30, and 20 percent per year of deaths from cancer of the bladder, larynx, esophagus, and breast, respectively. Several papers are cited as the sources of these estimates. However, the uncertainty in these values is not addressed, nor is the fact that in other studies some of the observed effects were not confirmed. The review article on β-carotene by Peto *et al.* (*2*) states that the many observational studies of dietary factors and cancer incidence have indicated "a slightly lower than average incidence of cancer among people with an above average intake of β-carotene." Weinstein's estimates of the percentages of cancer deaths averted per year do not appear to be consistent with this statement.

Weinstein also estimates the "prior probability that *p*-dichlorobenzene is a carcinogen" to be 10 percent. The negative results of the chemical in the Ames assay are cited. Yet the positive and equivocal results in other short-term tests are not mentioned, nor is the fact that the International Agency for Research on Cancer evaluated the evidence from short-term tests to be inadequate (*3*). Similarly, no mention is made of the case reports of blood disorders after exposure to *p*-dichlorobenzene (*4*). Such findings could have significant impact on the prior probability of carcinogenicity.

Weinstein chooses β-carotene and *p*-dichlorobenzene as best case examples. Given the extensive nature of animal and epidemiologic testing, β-carotene clearly qualifies. However, a number of other industrial chemicals would have been better examples than *p*-dichlorobenzene. One of these is toluene, which was designated a priority chemical for consideration for industry-required testing by the Interagency Testing Committee in its first report to the administrator of the Environmental Protection Agency (EPA) (*5*). More than 5 billion pounds of this chemical are produced annually; and it is used as a solvent, a component of gasoline, and a chemical intermediate in the manufacture of a variety of products. It has been estimated that more than 4 million workers have been exposed to toluene, and the number of consumers exposed is also significant (*6*).

When one considers the cost-effectiveness of animal cancer studies, one should also take into account the fact that these studies are now designed to yield information on additional types of long-term toxic effects induced by the chemical being tested. Similarly, in clinical trials, the potential risk of adverse human effects should be evaluated. Although the risks may be quite small, were adverse effects to ensue, the resulting costs would be significant and would alter cost-effectiveness calculations.

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2. R. Peto, R. Doll, J. D. Buckley, M. B. Sporn, *Nature (London)* **290**, 201 (1981).
3. *IARC (Int. Agency Res. Cancer) Monogr. 29* (1982).
4. R. Girard, F. Tolot, P. Martin, I. Bourret, *J. Med. Lyon* **50**, 771 (1969).
5. TSCA Interagency Testing Committee, *Fed. Regist.*, 12 October 1977, p. 42FR55026.
6. "Toxic substances; Toluene; Response to the Interagency Testing Committee, Environmental Protection Agency," *ibid.*, 16 December 1982, p. 47FR56391.

Bailey and Rall raise some important issues regarding my proposed approach to setting research priorities in cancer prevention. Some of their concerns relate to the validity and structure of the model; others pertain to the particular estimates that I used in the illustrative application of the model to the bioassay of *p*-dichlorobenzene and the clinical trial of β-carotene. I should like to respond to both kinds of concerns.

The model is intended to be used as a guide to prospective priority setting at a given time, given the information available at that time. Thus, the cost-effectiveness estimates for the β-carotene trial apply to the decision whether to conduct the trial, given the scientific database as it was at the time that decision was made. The expected costs and benefits are appropriately calculated from that point forward. It is irrelevant to that decision whether $18 million or $18 billion had been spent in the past to reach that point.

The approach can also be applied, in principle, to decisions about research at an earlier stage in the scientific process, for example, as Bailey suggests, to decisions about research on indole-3-carbinol and other plant phenolics. In such cases, the costs of basic research must be considered, but the possibility of unanticipated spin-off benefits cannot be ruled out either. In the particular case of β-carotene, it should be observed that the research expenditures might not have reached $18 million had interim results not been promising, thus progres-

sively increasing the prior probabilities of success along the way. In retrospect, adding an expenditure of $\$18 \times 10^6$ on β-carotene research (Bailey's estimate) to the $\$4 \times 10^6$ for the trial still leaves the enterprise looking extremely cost-effective, even if the only benefit of that research had been to identify β-carotene as a potential human anticarcinogen.

As stated in my article, I agree with Rall's observation that bioassays may have value in developing a scientific database for future priority-setting. I would take issue only with his conclusion that testing is, therefore, "necessary." Priorities do need to be set, and we must not lose sight of the primary objective of protecting the public health. In the same vein, I agree that negative studies may have value, but urge only that we be explicit that the value of such study results is "confidence" or reassurance and not cancer prevention. Indeed, one advantage of an explicit approach to priority-setting is to reveal the value judgments and beliefs that motivate a decision to perform any given study.

The fact that β-carotene is one of only a few dietary constituents that are ready for trials does not diminish the conclusion about the cost-effectiveness of that trial. Certainly I am not prepared to argue that all such trials of dietary constituents would be as cost-effective. However, recent epidemiologic and laboratory findings do suggest that rather large investments in applied research on dietary agents are likely to be cost-effective (*1*).

By the same token, the bioassay of *p*-dichlorobenzene may not be the most cost-effective among all those of industrial chemicals. However, the dichlorobenzenes, not toluene, were selected by the EPA from among the first set of nominees by the Interagency Testing Committee to be the subject of the first draft testing rules advanced by EPA. (No draft rules have yet been made final.)

As for the particular estimates of the percent reduction in cancer mortality with β-carotene, I stand by my estimates as consistent with Peto's review (17 of 20 studies he reviewed found relative risk of 1.3 or greater in the target organs examined) and subsequent studies. One advantage of my proposed approach is that it invites those who have different judgments to enter those in the model. Nonetheless, as demonstrated by the sensitivity analysis in my article, even if the estimates of cancer reduction were believed to be overstated by a factor of 2, 3, or more, the basic conclusions of the analysis would stand. Indeed, if β-carotene reduces cancer mortality by only a few percent, the major drawback to the trial would not be the size of its potential health impact (which would still be great) but its ability to detect such a small relative mortality difference.

The model is intended to be a guide to decision-making in the face of uncertainty and resource constraints, not a source of scientific truth. Thus, its conclusions in any particular instance should not be regarded as cast in stone and may change as new data become known. Moreover, scientists may disagree about the estimates entering into the model. (For example, it is my personal judgment that, absent any particular structure-activity hypothesis or ominous short-term test results, the prior probability that *p*-dichlorobenzene is a human carcinogen is not more than 10 percent. Rall's opinion is different and should be reflected in his use of the model.) What is important is that these underlying judgments be made explicit and debated openly in the priority-setting process. I am delighted that this model has already begun to stimulate such explicit, open discussion.

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1. B. N. Ames, *Science* **221**, 1256 (1983).

The Cover's Message

I couldn't disagree more with James C. Nofziger (Letters, 4 Nov., p. 456): I had no trouble distinguishing the message in the cover of 23 September from the burden of the article by Bruce N. Ames (23 Sept., p. 1256). The cover, crudely literated, says, "there are interesting, surprising, and paradoxical relationships between eating and dying." In its present context, it also says, "to learn about some of them, look in this magazine." I think this is a fine way for a cover to function, even on a scientifically objective journal.

More generally, I think your covers are often remarkably witty and subtle (wit and subtlety are important to good science), especially the last two Halloween covers and last year's Christmas cover.

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