noma in both sexes; by 31% for female breast cancer; by 92% for testis cancer; by 67% for prostate cancer; and by 63% for colorectal and 142% for kidney cancers in males (*26, 28*).

Apart from fundamental problems inherent in Ames's views on carcinogenesis and his dismissal of concerns about industrial carcinogens as "chemophobia," positions editorially endorsed (*29*), his current views and recommendations contrast strikingly with those previously and strenuously propounded (*30*).

Besides proper concerns about naturally occurring carcinogens and tobacco, prudent policy must reflect overwhelming data on incremental exposure to industrial carcinogens and their association with increasing cancer rates, besides reproductive, neurotoxic, and other toxic effects (*31*). The existence of natural hazards clearly does not absolve industry and government from the responsibility for controlling industrial hazards. From public health, ethical, and policy perspectives, the important distinction is not between "natural" and "synthetic" carcinogens, but between preventable and nonpreventable cancers.

SAMUEL S. EPSTEIN
University of Illinois Medical Center, Chicago, IL 60680
JOEL B. SWARTZ*
University of Quebec, Montreal H3C-3P8, Canada

*Cosigners: John Bailar, McGill University, Montreal; Eula Bingham, University of Cincinnati Medical School; Donald L. Dahlsten, University of California, Berkeley; Peter Infante, Washington, DC; Philip Landrigan and William Nicholson, Mount Sinai School of Medicine, New York; Marc Lappé and Michael Moreno, University of Illinois Medical Center; Marvin Legator, University of Texas Medical Branch, Galveston; Franklin Mirer, Rafael Moure, and Michael Silverstein, United Auto Workers, Detroit; David Ozonoff, Boston University Medical School; Beverly Paigen, Oakland Children's Hospital, Oakland, CA; and Jacqueline Warren, Natural Resources Defense Council, New York.

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30. In 1977, Blum and Ames warned that the synthetic carcinogenic pesticide ethylene dibromide (EDB) is a "potent carcinogen" whose structural similarity to the flame retardant tris is one of the reasons why the synthetic chemical tris "should not be used." They also pointed to "enormous possible [carcinogenic] risks" from using an untested chemical in [a fire retardant in] pajamas, predicted that a "steep increase in the human cancer rate from these suspect . . . chemicals may soon occur" "as the 20- to 30-year lag time of chemical carcinogenesis in humans is almost over," [A. Blum and B. Ames, *Science* **195**, 17 (1977)]. Blum and Ames also emphasized the need for high-dose testing in an effort to compensate for the "inherent statistical limitation in animal cancer tests" and expressed concerns about "the effects of the large-scale human exposure to the halogenated carcinogens [including] vinyl chloride, Strobane-toxaphene, aldrin-dieldrin, DDT, trichloroethylene . . . [and] heptachlor-chlordane." In 1979, Ames and his colleagues demonstrated that carcinogenesis dose-response curves usually rise less steeply than linear curves and criticized the view that many carcinogens have activity only at very high doses [W. Hooper, R. Harris, B. Ames, *ibid.* **203**, 602 (1979)]. Ames also stressed the need to establish "priorities for trying to minimize human exposure to these [synthetic] chemicals" [B. Ames, *ibid.* **204**, 587 (1979)]. Four years later, however, he reversed himself and concluded that cancer rates were not rising, that synthetic carcinogens posed only trivial risks, and that the real culprits were natural carcinogens and faulty life-styles, tobacco, and high-fat diets, citing Doll and Peto (*24*), who "guestimated" that diet, particularly fat, is incriminated in 35% of all cancer deaths, as the basis for this statement [B. Ames, *ibid.* **221**, 1256 (1983)]. Now, the carcinogenic hazards of high-fat diets are virtually dismissed in a few parenthetic words "[a possible risk factor in colon cancer . . .]," presumably reflecting Peto's recent reversal on the role of fat [R. Peto, *ibid.* **235**, 1562 (1987)], and in its place alcohol now emerges, alongside tobacco, as [one of the two] "largest indentified cause of neoplastic death in the United States."
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Response: We agree with only the last two sentences of the letter of Epstein *et al.* Correcting each of their errors would require lengthy explanations and would duplicate previous detailed analyses (*1–3*), so here we cover only the main issues.

■ *Half the chemicals tested in animals are carcinogens.* Our exhaustive database of animal cancer tests listed 392 chemicals tested in *both* rats and mice at or near the maximum tolerated dose (MTD). Of these, 60% of the synthetic chemicals and 45% of the natural chemicals were carcinogens in at least one species (*1*). The finding that about half of tested chemicals are positive in rodents has been reported for many sets of data; we cited among others the studies of the National Toxicology Program (NTP). We concluded that the proportion of chemicals found to be carcinogens is strikingly high. Epstein *et al.* ignore our data and citations and cite the early Innes *et al.* study to support their conclusion that the proportion of carcinogens is low. This misrepresents the facts. The Innes tests (120 chemicals, not 150 as stated by Epstein *et al.*, 11 positive) used only one species and were much less thorough than modern tests: they therefore were less likely to detect a carcinogenic effect (*4*).

The proportion of carcinogens is about as high for natural chemicals as for industrial chemicals. Therefore, our diet is likely to be

very high in natural carcinogens, since more than 99.99% of the pesticides we ingest are "nature's pesticides," chemicals that plants produce to defend themselves against insects, fungi, and other pests (*1*, *2*). These are present in all plants and in enormous variety, and their concentration is commonly in parts per thousand (*1*, *2*, *5*) rather than the parts per billion level of synthetic pesticide residues or water pollution (*1*, *2*). The known natural carcinogens in mushrooms, parsley, basil, parsnips, celery, figs, mustard, pepper, fennel, and citrus oil are just a beginning, since so few of "nature's pesticides" have yet been tested (*5*). Cooking food produces carcinogens (*1*, *2*) and so does our normal metabolism (*2*, *6*). A high proportion of the chemical elements tested are carcinogens. Epstein *et al.* do not address this problem. They do not acknowledge that at the MTD about one-third of all chemicals tested are teratogens (*1*), half of all chemicals are carcinogens, and many chemicals are mutagens; and these categories are not completely overlapping. Even when one considers that some chemicals are selected for testing because they are suspicious, these are strikingly high proportions (*1*, *4*).

■ *Extrapolating rodent cancer test results to humans.* The key issue, given the above facts, is how to identify *significant* preventable exposures to carcinogens (*1*, *7*, *8*). It is reasonable to assume that if a chemical is a carcinogen in rats and mice it is likely to be a carcinogen in humans at the same (MTD) dose. However, until we understand more about mechanisms, knowing the shape of the dose response in the dose range tested in laboratory animals provides little scientific basis for predicting the risk to humans at low doses, often hundreds of thousands of times below the dose at which an effect is observed in rodents (*9*). Thus, quantitative risk assessment is currently not scientifically possible (*1*, *7–10*).

Our HERP index uses the same toxicological information from animal bioassays that is generally used to estimate human risk, but is instead a relative ranking of the possible hazards of a variety of natural and synthetic chemical exposures to humans. We stated clearly that our HERP value should not be used to assess risks, because we do not know how to extrapolate to low doses. The HERP scale may be a way of putting possible hazards in perspective and of setting priorities for epidemiological testing and regulatory policy. Our ranking uses the same criteria for all exposures and indicates that there is a large background of natural and everyday exposures that rank high in possible hazard compared with exposures to pesticide residues or water pollutants. As we indicated in our article, one cannot say whether such natural exposures are likely to be of major or minor importance in human cancer. Our database of carcinogenic potency analyzes animal cancer tests and calculates the TD_{50}, essentially the dose of the carcinogen to give half of the animals cancer; the TD_{50} is close to the dose range tested in the laboratory animal. Our HERP is the dose (in milligrams per kilogram) to which humans are exposed, as a percentage of the TD_{50} dose.

Epstein *et al.* have three erroneous objections to our comparisons.

1) They say our HERP values are overestimates for natural chemicals relative to synthetic chemicals because (i) dose-response curves flatten out at high doses and therefore linear extrapolations underestimate low-dose risks, and (ii) natural chemicals are more thoroughly studied (at lower doses) than are synthetic chemicals. Neither (i) nor (ii) is true. As we discussed in our article, there is no way to calculate a low-dose risk from the two dose levels tested in an animal bioassay. In addition, our analysis of the animal dose-response curves indicated a better fit with a quadratic model (upward curving) than with a linear model, and that flat dose-response curves (supralinear) are a rarity. Synthetic chemicals are not less well studied than natural chemicals, as can be seen from our published database: 80% of the studies are on synthetic chemicals; most of the studies referred to were National Cancer Institute (NCI)–NTP tests done at the MTD and at half the MTD; the few chemicals tested at a wider range of doses are not biased toward natural chemicals.

2) Epstein *et al.* say we ignore the fact that plants contain anticarcinogens. We do discuss this fact (*1*, *2*), and it does not support their argument that this affects our comparisons: plant antioxidants, the major known type of ingested anticarcinogens, help to protect us against oxidant carcinogens *whether synthetic or natural in origin.*

3) Epstein *et al.* say natural carcinogens can be synergistic with other substances. However, this is also true of synthetic chemicals, and it is also irrelevant to our argument that synthetic pesticide residues in food or water pollution appear to be a trivial increment over the background of natural carcinogens.

■ *Carcinogenesis mechanisms and the dose-response curve.* We discussed the rapidly developing field of mechanisms in carcinogenesis because this understanding is essential for rational risk assessment. Cell proliferation (promotion) and mutation are involved in carcinogenesis, with a basal spontaneous rate for each step (*6*, *11*, *12*). Thus, increasing either rate increases the chance of cancer. In addition, several mutations appear necessary, and we have many layers of defense against carcinogens. These considerations of mechanism suggest a sublinear dose-response relation, which is consistent with both the animal and human data (*1*). It also suggests that multiplicative relationships may be the norm in human cancer causation. Administering chemicals in cancer tests at near-toxic doses (the MTD) commonly causes cell proliferation (*9*). If a chemical is nonmutagenic, but is carcinogenic because of its toxicity, then it should have no effect at low doses. This is a major point (*1*). Epstein *et al.* raise two points concerning the above that we find erroneous.

1) They say we should not call promoting agents carcinogens. However, well-studied promoting agents have been shown to cause cancer by themselves, as do those hormones that cause cell proliferation (*11*). In fact, this class of carcinogens may well include the most important risk factors for human cancer (*1*, *8*, *11*, *12*).

2) Chronic irritation as a risk factor for cancer is not "a discredited theory," but is supported by rodent and human evidence, and by recent evidence on cancer mechanisms indicating that cell-killing causes both cell proliferation and a mutagenic burst of oxygen radicals (*1*).

■ *Factors important in causing human cancer.* The major risk factors of tobacco (30% of U.S. cancer), dietary imbalances, hormones, and viruses appear to account for the bulk of human cancer (*1*, *3*, *7*, *8*, *11–13*). In our article we analyzed the evidence from animal cancer tests that was relevant to some of these risk factors and to occupational exposures and pollution.

Epstein *et al.* distort our discussion of the role of dietary fat and calories in cancer causation. Limiting calories in rats or mice (compared with ad libitum consumption) *reproducibly* extends life-span and decreases spontaneous tumor rates. Caloric intake is likely to be a significant risk factor in human cancer causation (*11*, *14*). Excess saturated fat consumption is a clear risk factor for heart disease. Excess fat consumption is a plausible, but not proved, risk factor in several types of human cancer, a view supported by extensive animal evidence (*1*, *3*, *12–14*). However, disentangling the effect of excess fat from excess calories is difficult in both rodents and humans (*14*).

Alcohol consumption is certainly the major known chemical risk factor for birth defects and is thought to account for 3% of U.S. cancer (*15*). Epstein *et al.* discount the importance of alcohol because it is synergistic with smoking. They are inconsistent, because they do not discount the effects of radon, asbestos, or other occupational exposures that are also synergistic with smoking.

For example, they attribute deaths to asbestos (exaggerated), but do not mention that the risk of lung cancer for asbestos workers would be an order of magnitude less if workers did not smoke. It is more reasonable to apportion, rather than to dismiss, these risks.

Occupational exposures to chemicals and possible hazards can be high, as we showed in our article. But the sweeping statements made by Epstein *et al.*, without a discussion of dose, do not clarify matters. In a separate analysis (*16*) we have ranked the potential carcinogenic hazards to U.S. workers using the PERP index (analogous to the HERP index except that Occupational Safety and Health Administration Permitted Exposure Levels replace actual exposures). The PERP values differ by more than 100,000-fold. For 12 substances, the permitted levels for workers are greater than 10% of the rodent TD_{50} values. Priority should be given to reduction of the allowable worker exposures that appear most hazardous in the PERP ranking.

Epstein *et al.* misrepresent the conclusions of the NRC-NAS committee report on pesticides, which did not say there would be 1.5 million deaths from pesticide use; the report did not predict deaths from pesticide use at all (*17*). Our article showed that the actual levels of synthetic pesticide residues eaten in the United States are tiny relative to the background of natural pesticides in plants. The end result of disproportionate concern about tiny traces of synthetic pesticide residues, such as ethylene dibromide (*1*), is that plant breeders are breeding highly insect-resistant plants: this may create other risks (*18*).

Our conclusion that water pollution did not make toxicological sense as a significant cause of cancer (or birth defects) because the amounts involved were extremely small compared with the background levels, is not contradicted by the epidemiological studies cited by Epstein *et al.* It is almost always beyond the power of epidemiology to provide convincing evidence that clusters of cancer or birth defects are due to pollution or to chance, bias, or confounding variables (*7*). Epstein *et al.* discuss Woburn, Massachusetts, without mentioning severe criticisms of the study they cite (*19*). Our analysis showed that the polluted water in Woburn or in Silicon Valley was less of a possible hazard than the chloroform in average U.S. tap water, a minimal possible hazard itself compared with the background. Comparative toxicological analyses such as ours can help epidemiologists to set priorities in their efforts and to distinguish causal correlations from the myriad of chance correlations. For example, the intake of burnt material from outdoor air pollution is so tiny compared with that from smoking (or from cooking food) that it seems implausible as a major source of cancer, a view consistent with the epidemiology cited, and indicates that epidemiologists must rigorously control for smoking (*20*).

■ *Cancer trends.* In our article we discussed cancer trends only in passing, but others have dealt with them in greater depth than do Epstein *et al.* (*3, 21*). Our statement that cancer death rates were not increasing except for those due to tobacco (mainly lung) and ultraviolet light (melanoma) was based mainly on analyses by Doll and Peto (*3*). Their analysis did take into account blacks and people over 65: Doll and Peto also pointed out that although incidence rates are of interest, they should not be taken in isolation because of the substantial extent to which trends in the recorded incidence rates are biased by improvements in the level of *registration* and *diagnosis*, as appears to be the case with breast cancer. Even if particular types of cancer will be shown to increase or decrease (stomach, liver, and uterine cancer are decreasing), establishing a causal relation among the many changing aspects of our lives remains difficult (*3, 7, 11–13*). There is no good evidence that there is any general increase in cancer due to the modern industrial world (*3*).

Epstein *et al.* complain that one of us (B.N.A.) has modified his views in the last decades. In the rapidly changing and difficult area of cancer cause and prevention, not modifying one's views to keep up with new facts is a sure way to lose scientific credibility (*22*).

BRUCE N. AMES
Department of Biochemistry, University of California, Berkeley, CA 94720
LOIS SWIRSKY GOLD
Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720

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2. B. N. Ames, *ibid.* **221**, 1256 (1983).
3. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, Oxford, England, 1981).
4. J. R. M. Innes *et al.* [*J. Natl. Cancer Inst.* **42**, 1101 (1969)] used two mouse strains (versus two species for NCI-NTP), had only 17 animals per group (versus 50 for NCI-NTP), had only one dose level (versus two for NCI-NTP), and were 18-month experiments (versus 24-month for most NCI-NTP); the dose was likely below the MTD (among 19 Innes chemicals also tested by another laboratory, the Innes dose was usually lower, sometimes by more than tenfold). We have discussed positivity in animal cancer tests in detail, including the Innes design (L. S. Gold *et al.*, *Environ. Health Perspect.*, in press).
5. For example, a recent analysis of lima beans showed an array of 23 natural alkaloids (those tested have biocidal activity) that ranged in concentrations in stressed plants from 0.2 to 33 parts per thousand fresh weight. None appear to have been tested for carcinogenicity or teratogenicity [J. B. Harborne, in *Natural Resistance of Plants to Pests. Roles of Allelochemicals*, M. B. Green and P. A. Hedin, Eds. (ACS Symposium 296, American Chemical Society, Washington, DC, 1986), pp. 22–35].
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15. Ethyl alcohol itself (15 grams per drink) is the likely teratogen and carcinogen in alcoholic beverages [B. N. Ames, "Review of evidence for alcohol-related carcinogenesis" (report for Proposition 65 meeting, Sacramento, CA, 11 December 1987)]. The dose response in humans is of considerable interest: four drinks per day is associated with increased cancer and birth defects, yet one drink per day (the U.S. average) has not clearly been associated with increased risk. Both orange juice and bread naturally contain considerable amounts of alcohol.
16. L. S. Gold *et al.*, *Environ. Health Perspect.* **76**, 211 (1987).
17. At the press conference on the report, Arthur Upton, speaking for the committee, responded to a question by saying that the worst-case scenario possible might implicate pesticides in 400 cases of cancer per year at the present time. The worst-case scenario pictures every farmer using the maximum possible amount of every pesticide allowed, the public consuming this food for a lifetime, and a worst-case linearized multistage model for predicting risk. Since all of these worst cases appear much too pessimistic, an actual risk close to zero is more likely.
18. A recent case is instructive. A major grower introduced a new variety of highly insect-resistant celery into commerce. A flurry of complaints to the Centers for Disease Control from all over the country soon resulted when people who handled the celery developed a severe rash when they were exposed to sunlight. Some detective work uncovered that, instead of the normal level of 900 parts per billion of psoralens (light-activated carcinogens and mutagens), the pest-resistant variety contained 9000 ppb of psoralens. It is unclear whether other natural pesticides in the celery were increased as well. [S. F. Berkley *et al.*, *Ann. Intern. Med.* **105**, 351 (1986); P. J. Seligman *et al.*, *Arch. Dermatol.* **123**, 1478 (1987).]
19. W. Lagakos *et al.*, *J. Am. Stat. Assoc.* **81**, 583 (1986). The same issue contains articles by other epidemiologists critical of this study.
20. Epstein *et al.* cite an estimate that air pollution is a causal factor in 21% of lung cancer. This is not supported by other epidemiology. The cited study was not peer-reviewed and did not take into account important confounding variables [see (*3*)].
21. *Annual Cancer Statistics Review Including Cancer Trends: 1950–1985* (National Cancer Institute, Bethesda, MD, January 1988).
22. In this context the comments of two eminent epidemiologists on Epstein's writings are enlightening [(*7*); R. Peto, *Nature* **284**, 297 (1980)].

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