Letters

Carcinogens and Human Health: Part 1

Bruce N. Ames and Lois Swirsky Gold (Perspective, 31 Aug., p. 970) posit that most human exposure to synthetic chemicals that are rodent carcinogens poses little or no risk of cancer. They argue that the high doses used in rodent bioassays cause tumors largely by inducing cytotoxicity with resultant compensatory cell proliferation (mitogenesis) that converts DNA damage (mostly caused by endogenous compounds in food) into mutations. In their view, mitogenesis dominates the carcinogenic process with the result that thresholds exist for "nongenotoxic" rodent carcinogens, and the dose-response curve for genotoxic carcinogens is sublinear. They conclude that the current U.S. regulatory policy, which calls for controlling involuntary exposures to industrial chemicals and pesticides identified as carcinogenic in the laboratory, imposes unnecessary costs on society and conveys no benefit in terms of health protection. Thus they dismiss the potential risks from the more than 1 billion pounds of pesticides and related products produced annually in the United States and the estimated 22.5 billion pounds of toxic chemicals released or disposed of each year in this country (*1*).

These arguments are not new (*2*). Thus far, however, lengthy deliberations by U.S. and international health protection agencies, scientific advisory boards, and panels of experts have rejected proposals to relax standards for carcinogens and have supported the use of animal tests as predictors of effects in humans (*3*). U.S. agencies involved in risk assessment policy have adopted the general assumption of low-dose linearity for carcinogens—regardless of their presumed mechanism of action.

The rationale for these decisions is threefold: (i) the lack of adequate understanding of mechanisms by which carcinogens (especially those termed "nongenotoxic") exert their effect; (ii) the absence of an identifiable threshold or safe level of exposure for a diverse human population; and (iii) the desirability of preventing cancer through the use of testing in model systems, obviating the reliance on epidemiologic data in humans. This rationale remains valid in light of current knowledge.

First, a large body of data on chemical carcinogenesis and the molecular biology of cancer supports a far more intricate mechanistic explanation of tumor induction by both nongenotoxic and genotoxic carcinogens than one which is dominated by mitogenesis. Available rodent bioassay data do not show a consistent correlation between organ toxicity at the target site and carcinogenicity (*4*). Moreover, there are few cases of rodent carcinogens that are positive only at the high dose (*4–5*). In addition, not only does epidemiology fail to show a threshold at the lower bound of exposure to carcinogens in the workplace, but low-level community exposures to "occupational carcinogens" such as arsenic have resulted in increased incidence of cancer (*6*).

On another level, the multistage process of cancer development is known to involve both mutagenic and nonmutagenic mechanisms. These result in the induction of multiple direct and indirect genetic changes at target oncogenes or tumor suppressor genes as well as alterations in signal transduction pathways involved in growth control (*7*). There is no evidence that these molecular events occur only at high, toxic doses (*8*). Despite recent exciting advances in the molecular biology of cancer, many uncertainties remain.

In light of the uncertainty about mechanisms and human dose-response, the assumption of low-dose linearity for carcinogens continues to be a reasonable one (*9*). It is consistent with the fact that humans are exposed to multiple carcinogens, capable of additive and even multiplicative effects. It is also a prudent assumption given the striking interindividual variation in the biologic response to carcinogens. Recent studies show an impressive range of human response to xenobiotics in terms of the activation and detoxification of carcinogens, covalent binding to DNA, and DNA repair (*10*). Such findings argue against the concept of a single population threshold for a carcinogen.

The large and growing burden of cancer in the United States (now at 500,000 cancer deaths per year) vividly demonstrates the need for prevention. Prevention has always been the guiding principle in toxicology and public health policy and now merits increasing emphasis (*11*). Prevention means not only addressing those cancer risks already established as "major" contributors to the disease burden (such as smoking) and researching new potential "major" risks, as Ames and Gold suggest, but also reducing current involuntary exposures to identified industrial carcinogens (*12*). Indeed, on the basis of a highly simplified (called "HERP") system for ranking carcinogens developed by Ames and Gold, the estimated range of risk for "natural" and man-made carcinogens is comparable (13). While it is tempting to simplify the regulatory process for carcinogens, one can do so only by ignoring the complex biology and etiology of the disease itself.

FREDERICA P. PERERA
Division of Environmental Sciences, Columbia University School of Public Health, 60 Haven Avenue, B-109, New York, NY 10032

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5. J. E. Huff and J. K. Haseman, *Chem. Eng. News*, in press; testing is generally carried out at several doses, including the maximum tolerated dose (MTD) and fractions thereof. The MTD is selected to be minimally toxic. Although the experimental dose levels are generally considerably higher than human exposure levels, in a number of cases (ethylene dibromide, dibromochloropropane, methylene chloride, phenacetin, 1,3-butadiene, and benzine), the doses that induced tumors in rodents were comparable to human exposures (J. E. Huff and J. K. Haseman, *ibid.*).
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11. Support for relying on the animal bioassay in prevention comes from the observation that all 37 known human carcinogens, which have been adequately tested in rodents, have produced positive results in at least one animal species [*Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs* (International Agency for Research on Cancer, Lyon, France, 1988), vols. 1–42, suppl. 7]. Indeed, the animal data often predated human epidemiologic evidence. Had preventive action been taken on the basis of the preexisting experimental evidence, thousands of cancer deaths from carcinogens such as 4-aminobiphenyl, vinyl chloride, bis-

(chloromethyl) ether, and diethylstilbestrol could have been avoided.
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Response: Perera neither summarizes our views accurately nor acknowledges the evidence that contradicts the assumptions of the "toxic chemicals from industrial pollution" view of cancer causation and worst-case, low-dose risk assessment models (*1–3*).

Perera's statements about what we think is causing the enormous endogenous DNA-damage rate from oxidants are incorrect; it is from normal metabolism (*4*), not from "endogenous compounds in foods." This oxidative damage helps explain the epidemiological findings that lack of sufficient dietary antioxidants from fruits and vegetables appears to be a major contributor to various types of cancer, heart disease, cataracts, and other degenerative diseases that come with aging (*5*). Oxidants are also produced in large amounts during inflammation, and oxygen radicals are a stimulus for cell proliferation, that is, the wound-healing response. Antioxidants protect against all of these effects. We think that dietary imbalances such as folate (*6*) and antioxidant deficiencies are major contributors to human cancer.

The natural world makes up the vast bulk of chemicals that humans consume each day in both weight and number: ~1500 milligrams of natural plant pesticides and ~2000 milligrams of chemicals from cooking food, compared with 0.09 milligram of synthetic pesticide residues and a smaller amount of water pollutants (*2*). We have discussed why the toxicology of synthetic and natural chemicals is not fundamentally different (*3*). All chemicals are "toxic chemicals" at some dose, not just by-products of industry.

About half the *natural* chemicals tested chronically in rats and mice at the maximum tolerated dose (MTD) are carcinogens (*1, 3*). These tests on natural chemicals are the control for the high-dose toxicology in which a high percentage of all chemicals test positive (*3*). Since similar percentages of natural and synthetic chemicals are positive, one cannot just assume that every industrial pollutant is a potential time bomb, while every natural chemical is likely to be harmless. In roasted coffee, among 22 chemicals tested, 16 were rodent carcinogens. Thus one cup of coffee contains 10 milligrams of known rodent carcinogens, about equivalent in weight to the potentially carcinogenic synthetic pesticide residues one eats in a year (assuming half of the untested synthetic residue-weight will be carcinogenic in rodents) (*1*). There is every reason to expect that the thousand other chemicals in roasted coffee would produce a plethora of rodent carcinogens if tested at the MTD. This is also likely to be true of the many thousands of natural pesticides in plant foods (27/52 natural pesticides tested are rodent carcinogens) (*2*). Possible carcinogenic hazards from the few natural chemicals tested often rank much higher than those from pesticide residues or water pollution (*2, 7*). Thus there is no theoretical reason or convincing epidemiological evidence (*8*) that pesticide residues or water pollution are significant causes of cancer. Chemicals, whether natural or synthetic, are unlikely to be of importance at levels tens of thousands of times below the MTD. Occupational exposures, in contrast, can be very high and significant (*9*).

Citation of the paper by D. G. Hoel *et al.* (*10*) as evidence against a role for mitogenesis in carcinogenesis ignores the fact that cell proliferation was not measured. Moreover, assessing which lesions may actually represent a toxic response is largely subjective, particularly from routine histopathology done only at the end of an experiment. Another critical complexity is that mutation through mitogenesis is not of interest in cells that are discarded (for example, from epithelial tissues) or killed (from apoptosis). It is not toxicity that is important, but chronic mitogenesis in nondifferentiated cells that are not discarded; also, mitogenesis can occur without toxicity (*1*).

Perera indicates that the assumption of low-dose linearity for carcinogenesis is reasonable: we present numerous findings to the contrary (*1*). It is well documented by geneticists that cell division is an important factor in mutagenesis and can be of dominant importance for loss of heterozygosity through mitotic recombination or nondisjunction (*1*). Understanding the role of mitogenesis in mutagenesis and that of increased mitogenesis in tests at high doses helps one understand the upward-curving dose responses with diethylnitrosamine, formaldehyde, 2-acetylaminofluorene, and saccharin (*1, 11*). Such an understanding can also explain the result that half of the chemicals tested at the MTD are carcinogens and that about 40% of these are apparently not genotoxic (*1*). Several recent findings indicate an important role for mitogenesis. These include the experiments of M. L. Cunningham *et al.* (*12*) that compare carcinogenic and noncarcinogenic isomers of mutagenic compounds and show that mitogenesis is increased only in the carcinogenic isomer; the study of H. A. Dunsford *et al.* (*13*) of transgenic mice that overproduce one protein of the hepatitis B virus increases cell turnover: all the mice develop hepatocellular carcinomas; the finding that caloric restriction in rodents lowers both rates of mitogenesis and spontaneous tumor rates (*14*); the role of mitogenesis in several types of human cancer; and more (*1*). DNA adducts are not the same as mutations, and a linear dose-response for adducts will not be a linear dose-response for mutagenesis or carcinogenesis when mitogenic effects are nonlinear. Carcinogenesis models that include the effects of mitogenesis make more biological sense than those that do not (*15*).

Perera discusses low levels of chemicals causing cancer, but chemicals are rarely tested at doses below the MTD and half the MTD. Moreover, about half of the positive sites in animal cancer tests are not statistically significant at half the MTD. With only two doses and a control in cancer tests, information about dose response shape is limited. Even at these high doses, however, a quadratic dose response is compatible with more of the data than a linear one for both mutagens and nonmutagens, and a plateau in the dose response (which could indicate a super carcinogen) is uncommon (*16, 17*).

Perera's evidence that a "low level of community exposure to 'occupational carcinogens' . . . resulted in increased incidence of cancer" is from a paper (*18*) whose authors examine "residence in areas with heavy levels of arsenic and cadmium." The study did not measure personal exposure, but levels in the soil; and after adjustment for smoking and occupation there was no statistically significant relative risk of lung cancer. In comparison, natural arsenic in U.S. water supplies may be the most important potential carcinogen in tap water (*19*). Both natural arsenic in water and natural radon in indoor air are present at high levels at some locations, and major efforts were put into miniscule amounts of industrial pollutants.

We agree with Perera that cancer prevention is important, but we would put more effort into studying carcinogenesis mechanisms and dietary imbalances and into encouraging the public to eat more fruits and vegetables and less animal fat.

Perera suggests that current policy attempting to protect the public at 10^{-6} hypothetical, worst case risk (~380,000 times below the MTD of a rodent carcinogen) (*20*) from industrial pollution, while ignoring the natural world is prudent, whatever the cost. We believe this is neither scientifically sound nor useful; it confuses regulators and the public as to what is important and diverts resources from more important risks and is therefore counterproductive (*21*). Pollution control is desirable (*22*), but can-

cer risk estimates at miniscule doses should not be a surrogate for the environment.

BRUCE N. AMES
Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720
LOIS S. GOLD
Carcinogenic Potency Database, Laurence Berkeley Laboratory, Berkeley, CA 94720

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The Avocado Illusion

An interesting review by Dennis R. Proffitt (28 Sept., p. 1590) of the book *The Moon Illusion* by Maurice Hershenson calls to mind a strong and possibly related illusion that I have not seen described previously.

At the risk of having this observation mistaken for buffoonery, I refer to the apparent size of avocados and other fruit which, when overhead in the tree, appear 20 to 50% larger than when brought down to eye level. I have noticed this for several years and have discussed it with other lay observers who confirm the illusion. Some of the effect should undoubtedly be attributed to disillusion rather than illusion. However, I find a similar effect with a tennis ball hung in the upper branches.

The fact that this "avocado illusion" is exactly the opposite of the moon illusion is an intriguing aspect that should be of interest to students of experimental psychology.

Although this report may generate a smile, it is not a canard. As illusions go, this one is very real. Or at least, it seems to be.

PAUL E. SANDORFF
121 West Avenida Cordoba, San Clemente, CA 92672

Erratum: In Marcia Barinaga's Research News article "Biology goes to the movies" (30 Nov., p. 1204), the journal *Anatomical Record* was incorrectly referred to as the *"Antomical Review"* at the end of the third column on page 1205.

Erratum: In the Erratum (7 Dec., p. 1320) about the Editors' response to George Legge's letter of 16 November (p. 889), the error was not corrected. Reference should have been made to a "300-nm beam spot," not a "300-μm beam spot."