Letters

Carcinogenicity of Aflatoxins

The generally well-presented articles and editorial in the "Risk Assessment" issue of *Science* (17 April) contain, by my count, 12 references to aflatoxin (a mold toxin, or mycotoxin) and one generalization about mycotoxins. Each reference is presented as an illustration of a point, but unfortunately much of the key information given is inaccurate and the reader may be left with an incorrect impression of the risk from aflatoxin and other mycotoxins and the management of that risk.

Richard Wilson and E. A. C. Crouch (p. 267) and Lester B. Lave (p. 291) imply a toxicological basis for the Food and Drug Administration (FDA) "action level" of 20 parts per billion of aflatoxins. In fact, that concentration was established in 1969, with no toxicological basis, as the lowest at which the identity of aflatoxin could be confirmed by the then available methods (*1*). Although improved methods now allow confirmation of identity (a prerequisite for legal action) at much lower concentrations, the "action level" has not been reduced.

Wilson and Crouch (table 3, p. 270), and Bruce N. Ames *et al.* (p. 271) state with varying degrees of certitude that aflatoxin is a human carcinogen, relying on outdated (Wilson and Crouch) or incomplete (Ames *et al.*) information; and Ames *et al.* (table 1, p. 273) list aflatoxin as a carcinogen for mice, an interpretation of the data that is questionable. The positive observations of liver malignancies in mice were from experiments in which large interperitoneal doses were used (*2*). Large doses given orally produced no tumors (*3*) (mice are generally considered to be refractory to aflatoxin carcinogenesis). Ames *et al.* could have discussed the considerable information on aflatoxin metabolism and pharmacodynamics (*4, 5*) in rats, mice, other susceptible and resistant species, and humans (in vitro) that points to between-species differences. The epidemiological evidence on which they rely for their conclusion "that aflatoxin is a human carcinogen" allowed a select committee of the International Agency for Research on Cancer, meeting in 1982, to conclude (*6*) only that the evidence for carcinogenicity in humans was limited, that is "a causal interpretation is credible, but alternate explanations such as chance, bias, or confounding could not be excluded." The studies on which this conclusion was based can be criticized (*4, 7*), and a confounding factor has since been determined to be chronic infection with hepatitis B virus (HBV). There is a strong association—an odds ratio of 223 for liver cancer in HBV carriers (*8*) compared with an odds ratio of 10 for lung cancer in cigarette smokers (*9*)—between liver cancer, the putative hazard from aflatoxin ingestion, and chronic infection with HBV (*10*) in areas of the world where liver cancer is encountered. The conclusion that aflatoxin is not a likely human carcinogen is supported by other independent studies of liver cancer (*7, 11*) and other cancers (*12*) in the United States. The current contention is that aflatoxin intoxication may interact with chronic HBV infection to produce liver cancer (*13*), but the evidence is not persuasive.

Ames *et al.* state (p. 273) that "[c]onsidering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they represent the most significant carcinogenic pollution of the food supply in developing countries." This subject has been reviewed (*14*). Of those mycotoxins likely to be contaminants of foods, only aflatoxin, ochratoxin A, patulin, penicillic acid, zearalenone, T-2 toxin, and deoxynivalenol have been studied with any degree of thoroughness. Aflatoxin and T-2 toxin have been implicated in acute human toxicoses; no mycotoxin has been linked with a specific cancer in humans. There has been speculation that one or more trichothecenes (for example, T-2 toxin) may be related to esophageal cancer in some areas of Africa and Asia and that ochratoxin A may be a factor in the endemic nephritis observed in the Balkans. However, the risk of human injury from patulin, penicillic acid, and zearalenone has been found to be insignificant. Another 28 mycotoxins have been shown to produce a cellular aberration by some type of mutagen screening test. I believe that jumping to conclusions from such evidence is hazardous. Interest and enthusiasm can easily affect the unwary to the point that speculation changes to increasing degrees of certainty, with no change in material evidence. Scientists are not immune to this disease.

LEONARD STOLOFF
13208 Bellevue Street, Silver Spring, MD 20904

REFERENCES

1. L. Stoloff, *J. Assoc. Off. Anal. Chem.* **63**, 1067 (1980).
2. S. D. Vesselinovitch, N. Mihailovich, G. N. Wogan, L. S. Lombard, K. V. N. Rao, *Cancer Res.* **32**, 2289 (1972).
3. G. N. Wogan, *Methods Cancer Res.* 7, 309 (1973); D. B. Louria, G. Finkel, J. K. Smith, M. Buse, *Sabouraudia* **12**, 371 (1974).
4. L. Stoloff, in *Mycotoxins and Phycotoxins*, P. S. Steyn and R. Vleggaar, Eds. (Elsevier, Amsterdam, 1986), pp. 457–471.
5. W. F. Busby, Jr., and G. N. Wogan, in *Chemical Carcinogens*, C. E. Searle, Ed. (American Chemical Society, Washington, DC, 1984), pp. 945–1136.
6. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4 to IARC Monographs, Vols. 1–29* (International Agency for Research on Cancer, World Health Organization. Lyon, France, 1982), pp. 11 and 31.
7. D. J. Wagstaff, *Regul. Toxicol. Pharmacol.* **5**, 384 (1985).
8. R. P. Beasley, L-Y. Hwang, C-C. Lin, C-S. Chien, *Lancet* **1981-II**, 1129 (1981).
9. R. Doll and R. Peto, *J. Natl. Cancer Inst.* **66**, 1191 (1981).
10. B. S. Blumberg and W. T. London, *ibid.* **74**, 267 (1985); *Technical Report Series No. 691* (World Health Organization, Geneva, 1983).
11. L. Stoloff, *Nutr. Cancer* **5**, 165 (1983).
12. T. J. Mason, F. W. McKay, R. Hoover, W. J. Blot, J. F. Fraumeni, Jr., *HEW Publ. No. (NIH) 75-780* (Department of Health, Education, and Welfare, Washington, DC, 1975).
13. S. J. Van Rensburg *et al., Br. J. Cancer* **51**, 713 (1985).
14. L. Stoloff, in *Carcinogens and Mutagens in the Environment*, vol. 1, *Food Products*, H. F. Stitzh, Ed. (CRC Press, Boca Raton, FL, 1982), pp. 97–119.

Response: We and Stoloff are apparently in agreement that aflatoxin is a carcinogen in several species, and that species differ in their sensitivity. Although, as we indicated in our table, there are no positive experiments in mice that are suitable for calculation of TD_{50}, our "+" in mice is based on the evaluation of the International Agency for Research on Cancer that aflatoxin induces tumors in that species. The epidemiological data suggest that it is a human carcinogen in combination with hepatitis B virus, although we agree with Stoloff that the evidence is not of the same certainty as that linking smoking and cancer (*1*). What our HERP (*H*uman *E*xposure dose/*R*odent *P*otency dose) ranking points out is that at current levels of human exposure and given the potency in rats, the possible hazard of aflatoxin in a peanut butter sandwich is greater by 10 to 100 times than possible hazards from several environmental pollutants, including trichloroethylene in contaminated well water and ethylene dibromide residues in grain. Yet those synthetic contaminants are given greater regulatory scrutiny on the basis of the results of animal experiments and even in the absence of epidemiological data, indicating that they might be carcinogenic in humans. In extreme cases in the United States HERP values for aflatoxin reached levels of 6% of the TD_{50} dose, which seems to us reason for concern. We also stand by our statement on pollution by molds in developing countries. In addition, new mutagenic mold toxins in food are constantly being found when they are looked for, and it is reasonable to suppose many will be found to be carcinogenic (*2*).

We stress that it is important to view the possible hazard of aflatoxin from the perspective of the many everyday possible hazards of life and with the knowledge that there are a great many uncertainties in the use of animal bioassay data in extrapolation to humans. As we discussed at length, the promotional aspects of cancer are also critical, and it is likely that the hazard from aflatoxin will be much lower in the absence of some toxicity in the liver such as from hepatitis virus, alcoholic cirrhosis, or the maximum tolerated dose in rodents. Since the HERP values for synthetic pollutants, including pesticides, are usually an order of magnitude less than that from aflatoxin, concern over them should be even less.

BRUCE N. AMES
RENAE MAGAW
Department of Biochemistry, University of California, Berkeley, CA 94720
LOIS SWIRSKY GOLD
Lawrence Berkeley Laboratory, Berkeley, CA 94720

REFERENCES

1. H. Autrop, T. Seremet, J. Wakhisi, A. Wasunna, *Cancer Res.* **47**, 3430 (1987); S. V. Thomson *et al.*, *J. Appl. Environ. Microbiol.* **35**, 1150 (1978); S. J. Cheng *et al.*, *Carcinogenesis* **6**, 903 (1985).

Response: We generally agree both with Stoloff's letter and the response of Ames *et al.* However, we *were* aware that the reliability of the connection between human cancers and exposure to aflatoxin B1 has been called into question by the realization that a more important risk factor is infection with hepatitis B virus, which inevitably confounds the data. Nonetheless, we believe that the certainty for human carcinogenesis is high, although not absolute; it is certainly superior to the evidence for cancers caused by dioxin. The 20 parts-per-billion action level for aflatoxin in peanut butter may indeed have been set at a detection limit (although we do not like this practice). However, as Stoloff himself points out, it has *not* been reduced, although a modest, in our view inadequate, proposal to reduce it to 15 ppb was made in 1977 long after more sensitive detection equipment was available. The proposal was abandoned.

RICHARD WILSON
E. A. C. CROUCH
Department of Physics and *Energy and Environmental Policy Center, Harvard University, Cambridge, MA 02138*

Erratum: In table 1 of the article "Changes in the distribution of American family incomes, 1947 to 1984" by Frank Levy (22 May, p. 923), the first quintile (%) for 1949 was inadvertently omitted. It should have been 4.5.