Letters

Significance of Nitrosamines in Animal Diets

A recent News and Comment briefing (13 Oct. 1978, p. 192) concerned our report (*1*) that laboratory animal feeds may be contaminated with up to 50 parts per billion (micrograms per kilogram) of the carcinogen *N*-nitrosodimethylamine (NDMA).

A subsequent letter (8 Dec. 1978, p. 1034) from William Lijinsky challenges the significance of this finding. He takes issue with our concern that the NDMA might have synergistic action with other (test) carcinogens. He states, "There is little evidence of a detectable synergistic effect of nitrosamines in carcinogenesis, even when much higher doses are given . . . "; and, in the next sentence, he says, "I suggest that a study of chemical carcinogenesis and its literature would enable the scientists who made this report to place their findings in perspective."

We have indeed examined the literature and find several reports which describe positive synergistic effects of nitrosamines (*2*), including a 1977 review by Lijinsky himself (*3*). In this article he concludes a brief discussion of synergism between carcinogens by stating "Several experiments with nitrosamines have also shown this type of synergism in carcinogenesis."

Lijinsky further challenges the significance of our results by stating that " . . . its [NDMA] presence at this concentration in the diets of rats or mice could have no bearing on the outcome of any test." We agree that 50 parts per billion of NDMA in feed is unlikely *by itself* to cause significant tumor response in small numbers of rodents exposed from the time of weaning, as in the studies cited by Lijinsky. However, this may not be the case if larger groups or younger animals, or both, are used. For instance, Lijinsky has stated (*3*), "Fetuses are often much more sensitive to carcinogens than are children or adults." A soon-to-be-published article from the Sloan-Kettering Institute (*4*) demonstrates that as little as 10 parts per billion of NDMA included in the water supply of strain A/J mice during the whole fetal, weaning, and postweaning period up to 22 weeks of age causes a tripling in the lung tumor incidence from 8 percent to 23 percent. Whether or not one accepts this rather tumor-prone strain as an appropriate model (*5*), these studies clearly refute Lijinsky's claim that up to five times more NDMA "presents no measurable risk to experimental animals that live only 2 to 3 years."

GORDON S. EDWARDS
Cancer Research Division,
Thermo Electron Corporation,
Waltham, Massachusetts 02154
JAMES G. FOX
Division of Laboratory Animal
Medicine, Massachusetts Institute of
Technology, Cambridge 02139

References and Notes

1. D. H. Fine, I. S. Krull, D. P. Rounbehler, G. S. Edwards, J. G. Fox, paper presented at the Annual Meeting of the American Chemical Society, Miami, September 1978.
2. D. Schmahl, *Oncology* **33**, 73 (1976); A. Cardesa, P. Pour, M. Rustia, J. Althoff, U. Mohr, *Z. Krebsforsch.* **79**, 98 (1973); C. Hoch-Ligeti, M. F. Argus, J. C. Arcos, *J. Natl. Cancer Inst.* **40**, 535 (1968).
3. W. Lijinsky, *Chem. Eng. News.* **55**, 25 (27 June 1977).
4. L. M. Anderson, L. M. Priest, J. M. Budinger, *J. Natl. Cancer Inst.*, in press.
5. For a discussion, see M. B. Shimkin and G. D. Stoner, *Adv. Cancer Res.* **21**, 1 (1975).

Phenacetin Studies

Thomas H. Maugh II, in his article "Chemical carcinogens: The scientific basis for regulation" (Research News, 29 Sept. 1978, p. 1200), treats a topic of increasing importance to drug safety evaluation and exposure to toxic substances. Maugh appropriately states that there is a difficulty with epidemiological data, namely, " . . . most of the people involved have generally been exposed to a number of other potentially hazardous agents. It is thus difficult to develop evidence of carcinogenicity from epidemiology alone." Yet, he presents a tabulation of "chemicals known to be carcinogens in man" based, in some cases only on case reports or epidemiological *associations* with exposure without confirmatory data from animal studies.

The source material for this list is apparently the summary report of the Monograph Program of the International Agency for Research on Cancer by Tomatis *et al.*, published in *Cancer Research* (*1*). The article listed chemicals and industrial processes associated with cancer induction in humans based on two criteria: "(a) that there is evidence of human exposure and (b) that there is some evidence of carcinogenicity in experimental animals and/or some evidence or suspicion of human risk." Tomatis *et al.* indicated that two of the drugs listed, oxymetholone and chloramphenicol, were included on the basis of epidemiological data, and that no adequate test results for carcinogenicity in experimental animals were available. A third drug, phenacetin, was included because of clinical case reports, not on the basis of any extensive epidemiological evidence. The article further indicated that adequate test results in animals were not available for phenacetin. Adequate tests, however, have been conducted and the results are available.

In 1970, Bengtsson and Angervall reported (*2*) on 14 clinical cases in which tumors of the renal pelvis were observed in patients who reputedly had a history of prolonged analgesic abuse. After this report was published, the Wellcome Research Laboratories undertook a long-term carcinogenicity study in mice. Phenacetin alone and aspirin-phenacetin-caffeine analgesic mixtures were administered to mice at maximum tolerated doses. This study, in which two known carcinogens were used as controls, is on file with the Food and Drug Administration. Neoplasms of the urinary tract were not observed in any analgesic-treated animal, whereas they were observed in the controls.

Also, a summary has been published (*3*) of the "NCI [National Cancer Institute] report on the bioassay of a mixture of aspirin, phenacetin and caffeine (APC) for possible carcinogenicity" covering two additional studies. The report summary states, "After a 78-week period of compound administration, observation of the rats continued for up to an additional 35 weeks and observation of the mice continued for an additional 16 weeks. For both species the survival in all groups was adequate for statistical analysis of tumor incidence. Under the conditions of this bioassay there was insufficient evidence to indicate that APC was carcinogenic in Fischer 344 rats or in B6C3F1 mice."

These three independent toxicity studies involving lifetime exposure of large numbers of animals to maximum tolerated doses did not yield any positive evi-