Risk Analysis, 5, No. 4, 1985

Letter to the Editor

Toxicity and Carcinogenic Potency

Leslie Bernstein,[1] Lois S. Gold,[2] Bruce N. Ames,[2] Malcolm C. Pike,[3] and David G. Hoel[4]

In our recent paper,[1] we called attention to some of the points raised by Whipple and by Zeise, Crouch, and Wilson. Our interest in this subject developed as we began analyzing our database of animal carcinogenesis bioassays.[2,3] In our analyses, we used as a measure of carcinogenic potency, the TD_{50}, defined as the dose rate (in mg/kg/body wt/day) which, if administered chronically for a standard period, would halve the probability of an animal remaining tumorless. By analogy with LD_{50}, the TD_{50} is that daily dose which would induce tumors in half of the animals that would have remained tumor-free at zero dose. We demonstrated that the potency of a carcinogen is restricted to an approximately thirty-fold range, about the maximum dose tested in the experiment in the absence of 100% tumor incidence in treated animals.

The maximally tolerated doses (MTDs) of chemicals tested in chronic animal bioassays span a range of seven orders of magnitude, and these doses are highly correlated between rats and mice. These fact, together with the restricted range of potency about the MTD, (1) account for high correlations in carcinogenic potency between rats and mice, and (2) provide a statistical basis for the relationship between potency values and MTDs. One would expect to observe a similar relationship between carcinogenic potency (TD_{50}) and LD_{50}, assuming that the acute and the chronic toxic doses are related.

[1] Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California 90033.
[2] Department of Biochemistry, University of California, Berkeley, California 94720.
[3] Imperial Cancer Research Fund's Cancer, Epidemiology Unit, Radcliffe Infirmary, Oxford, England.
[4] National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

As we pointed out in our paper, there may well be a biological explanation for the observed relationship between carcinogenic potency and toxicity. As we stated:

> "If some compounds were highly carcinogenic compared with their MTDs, then we would expect to observe 100% (or at least very high) incidence rates at all of the experimental dose levels. This was not seen with the compounds under study. If the saturation of a metabolic activation process was involved, the dose response might plateau. From our database we observed that approximately 10% of the dose-response functions were sublinear, indicating possible saturation. For the compounds in which this was observed, it was, however, generally not replicated in other target sites in the same experiment, in the other sex of the same species, or in other species."
>
> "Biologically it may indeed be the case that TD_{50} and the MTD are closely related.[4] Tissue damage with cell killing and consequent cell proliferation has been shown to be important in the promotion of liver tumors and possibly other tumors as well.[5,6] Therefore, a single mutagenic compound given at tissue-damaging doses (near the MTD) can act as its own promoter as well as initiator. Thus, if cell killing shows an apparent threshold with dose, as is the case for several carcinogens in the liver,[7] then the carcinogenic potency near the MTD might be expected to be much greater than at non-toxic doses."

We would like to call attention to another reference [8] that supports the view that cell proliferation may enhance tumorigenesis in the pancreas, again emphasizing a plausible mechanism for a relationship between toxicity and carcinogenic potency. Human cancer is likely to be multicausal, as we are not generally taking in large doses of single chemical near the toxicity level. Thus, understanding the promotional risk factors for human cancer may be as important as understanding the initiating agents.

0272-4332/85/1200-0263$04.50/1

REFERENCES

1. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, and D. G. Hoel, "Some Tautologous Aspects of the Comparison of Carcinogenic Potency in Rats and Mice," *Fund. Appl. Toxicol.* **5**, 79–86 (1985).
2. L. S. Gold, C. B. Sawyer, R. Magaw, G. Backman, M. De Veciana, R. Levinson, N. K. Hooper, W. R. Havender, L. Bernstein, R. Peto, M. C. Pike, and B. N. Ames, "A Carcinogenic Potency Database of the Standardized Results of Animal Bioassays, *Environ. Health Perspect.* **58**, 9–319 (1984).
3. R. Peto, M. C. Pike, L. Bernstein, L. S. Gold, and B. N. Ames, "The TD50: A Proposed General Convention for the Numerical Description of the Carcinogenic Potency of Chemicals in Chronic Exposure Animal Experiments," *Environ. Health Perspect.* **58**, 1–8 (1984).
4. L. Zeise, R. Wilson, and E. Crouch, "Use of Acute Toxicity to Estimate Carcinogenic Risk," *Risk Anal.* **4**, 187–199 (1984).
5. E. Farber, "Cellular Biochemistry of the Stepwise Development of Cancer with Chemicals: G. H. A. Clowes Memorial Lecture," *Cancer Res.* **44**, 5463–5474 (1984).
6. C. C. Harris, and T. Sun, Multifactorial Etiology of Human Liver Cancer, *Carcinogenesis* **5**, 697–701 (1984).
7. E. Farber, S. Parker, and M. Gruenstein, "The Resistance of Putative Premalignant Liver Cell Populations Hyperplastic Nodules, to the Acute Cytotoxic Effects of Some Heptocarcinogens," *Cancer Res.* **36**, 3879–3887 (1976).
8. A. Denda, S. Inui, M. Sunagawa, S. Takahashi, and Y. Konishi, "Enhancing Effect of Partial Pancreatectomy and Ethionine-Induced Pancreatic Regeneration on the Tumorigenesis of Azaserine in Rats," *Gann.* **69**, 633–639 (1978).