

Letters

Wisdom of Cyclamate Ban

Inhorn and Meisner, in their letter "Cyclamate ban" (7 Nov.), refer to "overwhelming evidence that cyclamate causes no deleterious effect on humans [and they] . . . find it inconceivable that when there is so much human data available, that cyclamate be discarded on the basis of experiments employing only 12 rats." Such widespread misconceptions prompt this reply.

The editorial "Chemicals and cancer" by Abelson in the same issue properly refers to the difficulty of assessing carcinogenic hazards from chemicals because of the generally long interval between exposure and subsequent effect. For example, the average latent period is 18 years between occupational exposure to aromatic amine carcinogens and the induction of bladder cancer (1). As wide-scale dietary use of cyclamates is relatively recent, the retrospective Connecticut data, to which Inhorn and Meisner refer, indicating that there has been no increase in mortality from bladder cancer, are hardly relevant. In fact, the incidence of bladder cancer in Connecticut has increased in the last 20 years; in men it has approximately doubled (2). For the reasons given below, we endorse rigorous restriction of cyclamates.

In spite of a caution from the National Academy of Sciences in 1962 on the inadequacy of toxicological data on cyclamates (3), production in the United States increased from 5 million pounds in 1963 to 15 million pounds in 1967 and, if unrestricted use were to continue, would total an estimated 21 million pounds by 1970 (4). More recently, an interim report reemphasized this warning with particular reference to cyclohexylamine, a major human metabolite of cyclamate, and "recommended that adequate tests of carcinogenic potential of these materials and their metabolites be completed" (4, p. 49).

The ultimate decision to restrict cyclamates was based in part on the Abbott-sponsored 2-year study which indicated induction of bladder cancer in 7 of 20 male rats at risk following feeding with a mixture of cyclamate and

saccharin (10 : 1) at concentrations approximately 50 times greater than the estimated human exposure levels. This study can be reasonably criticized on the grounds that the rats should have been fed cyclamates only, but it cannot be criticized on the grounds that high dose levels were tested.

Let us assume that a carcinogen, such as a food additive or pesticide, at actual human exposure levels induces cancer in as many as 1 out of 10,000 humans, then the chances of detecting this in test groups of 20 to 50 rats exposed at these actual levels would be very low; indeed, many more than 10,000 rats, depending on their spontaneous tumor incidence, would be required to demonstrate a statistically significant increase in the cancer incidence if we assumed that rats and humans have similar sensitivity to the carcinogen being studied. For these reasons, it is routine practice to test for carcinogenicity at concentrations higher than human exposure levels. Apart from the Abbott data, reexamination (5) of the histopathology of the 1951 FDA chronic toxicity studies (6) suggests the carcinogenicity of cyclamates when tested alone. More recently, cyclamate salts fed to rats produced bladder cancer in 3 out of 23 rats and extensive hyperplasia and polyps in the bladders of 10 of 20 rats; no such changes were noted in comparable numbers of controls (7).

In addition to the legal basis for restrictions on cyclamates based on the Delaney Amendment, there are serious and unresolved questions as to the potential teratogenicity and mutagenicity of cyclamates. Data on the teratogenicity of both cyclamate and cyclohexylamine in the chick embryo (8) have to be contrasted with the lack of available mammalian data on the teratogenicity of cyclohexylamine. The demonstration of in vivo cytogenetic damage to rat germinal and somatic cells by microgram doses of cyclohexylamine is presumptive evidence of genetic hazard.

The decision to restrict cyclamates to the general public and to terminate a mass human experiment for which there are no demonstrable matching

benefits is clearly proper. We concur that food additives be banned from products unless they have been proven safe, and either significantly improve the quality or nutritive value of the food or lower the food cost (9). Finally, our experience with cyclamates emphasizes the critical need for reviewing procedures concerned with potential hazards due to chemicals to which we are currently exposed and which have never been adequately tested.

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References and Notes

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2. *Cancer in Connecticut, Incidence and Rates, 1935-1962; Cancer in Connecticut, Supplementary Mortality Data, 1949-1962; Cancer in Connecticut, 1963; Cancer in Connecticut, 1964* (Connecticut State Dept. of Health, Hartford).
3. *Policy Statement on Artificial Sweeteners* (Food and Nutrition Board, National Academy of Sciences, Washington, D.C., 1962).
4. *Interim Report on Non-nutritive Sweeteners* (Food Protection Committee, National Academy of Sciences, Washington, D.C., November, 1968).
5. Unpublished report on nonnutritive sweeteners by the Food Protection Committee, National Academy of Sciences, Washington, D.C. (16 October 1969), sec. 3, p. 51.
6. O. G. Fitzhugh, A. A. Nelson, J. P. Frawley, *J. Amer. Pharm. Ass.* **40**, 583 (1951).
7. Food and Drug Administration, unpublished data.
8. M. Legator, K. A. Palmer, S. Green, K. W. Petersen, *Science* **165**, 1139 (1969).
9. D. M. Kendall, *A Summary of Panel Recommendations*, Report of Panel on Food Safety to the White House Conference on Food Nutrition and Health (22 November 1969), p. 19.

Uphill Road for New Drugs

In "Prognosis for the development of new chemical birth-control agents" (24 Oct., p. 468), Djerassi is critical of the fact that appeals to rulings of the Food and Drug Administration (on clinical tests of contraceptives, for example) can be made only through the courts. He suggests that the ultimate authority should be vested with independent bodies of experts.

Judging the safety and efficacy of