Letters

Irresponsibility of Cyclamate Ban

While we concur with several of the statements in the letter "Wisdom of cyclamate ban" (26 Dec.), additional information that we have reviewed strengthens our opinion (Letters, 7 Nov.) that the cyclamate ban was irresponsible. We agree that experiments to determine carcinogenicity have to be long-term and that high dose levels must be used; however, we do not agree that valid conclusions can be based on utilization of small numbers of animals of a single strain, nor can we assume, as was stated by Epstein *et al.*, "that rats and humans have similar sensitivity to the carcinogen being studied." They also refer to the teratogenicity of both cyclamate and cyclohexylamine in the chick embryo, although these results have not been published. Moreover, cyclamate has not shown teratogenicity in any mammalian species. The letter also cites new results concerning bladder cancer in rats in an attempt to justify the cyclamate ban, but this information was not available at the time the ban was imposed.

Few compounds available today have been investigated as thoroughly as cyclamate. The Ad Hoc Committee on Nonnutritive Sweeteners of the National Academy of Sciences summarized research performed before November 1968 in detail and concluded: "From the work that has been reported, there is no evidence that saccharin or cyclamate poses a carcinogenic hazard" (*1*).

The Abbott-sponsored experiment, which provided the basis for the imposition of the cyclamate ban, involved feeding 240 rats one of three concentrations of a 10:1 mixture of cyclamate-saccharin daily for their lifetime; half of the animals being fed each concentration also received cyclohexylamine (a cyclamate metabolite) from the 79th week until the end of the experiment at 105 weeks. Bladder tumors were found in 7 of 20 males and 1 of 30 females who had received the highest dose of cyclamate-saccharin; three of these tumors were in the animals receiving supplemental cyclohexylamine and five in those that did not. At least four of the tumors were classified as carcinomas (true cancer), and only two tumors were visible without a microscope (*2*).

A significant finding was that only rats which had been fed the highest dose level of the cyclamate-saccharin mixture, 2500 milligrams per kilogram per day, developed bladder tumors (*2*). This dose level is roughly equivalent to the consumption of 350 bottles of diet drinks per day by a man weighing 70 kilograms. It is important to note that none of the rats which were fed intermediate levels of the cyclamate-saccharin compound developed bladder lesions. In establishing causation, one primary requisite is to demonstrate a dose-effect relationship, as was well documented with cigarette consumption in the report to the Surgeon General of the Public Health Service entitled *Smoking and Health* (1964). Another prime requisite in demonstrating causation is that only one chemical be tested at a time. In the Abbott experiment the substance tested was not pure cyclamate but 10 parts cyclamate to 1 part saccharin. How can the FDA and its expert advisory committee point the finger of blame at cyclamate and completely exonerate saccharin? Was it because cyclamate was the major ingredient? A true carcinogen is potent even in tiny amounts, although at 1/11th of 2500 milligrams per kilogram per day, the rats were getting a huge amount of saccharin. Yet saccharin was completely overlooked, even though it had not been thoroughly tested previously.

Some investigators have suggested that the carcinogenic compound may not be cyclamate, but its metabolite, cyclohexylamine. The rat experiment in which graded amounts of cyclohexylamine supplemented the cyclamate-saccharin feeding did not show a positive correlation between this compound and bladder tumors (*2*). In another experiment where 50 rats were fed high doses of just cyclohexylamine for 2 years, only one animal developed a bladder tumor (*2*). Thus it is not clear at the present time which of the three—cyclamate, cyclohexylamine, or saccharin—if any, are carcinogenic for the rat urinary bladder. Furthermore, rat bladders are not human bladders, and it is known that the rat bladder is not the target organ of many carcinogenic chemicals which cause bladder cancer in humans or dogs (*3*). For example, aromatic amines such as benzidine or beta-naphthylamine cause bladder cancers in humans and dogs, but are not carcinogenic for the rat bladder, while certain azo dyes which cause bladder tumors in rats are not carcinogenic for human or dog bladders (*3*). The point here is that metabolic or organ systems of different species may be very unique, and the results of rat experiments may have little if anything to do with human cancer.

Although we might agree with the merits of regulating the recommended total daily intake and, until more evidence is available, prohibiting cyclamate for children as is done with alcohol and cigarettes, on the basis of the data currently available we can see no reason for the total cyclamate ban and even less reason for having alarmed the American public by the sudden way in which the ban was imposed. Even if the ban were to be lifted, a great disservice has already been done in destroying public confidence in a compound which is not toxic even in massive doses and which has never been shown to cause cancer in man. After the summary nature of the ban, will diabetics, even on the advice of their physicians, want to use cyclamate?

We appreciate the role of the FDA in protecting the American consumer, but we feel that their decisions must be based on reliable standards, uniformly applied, and free of political pressure. Of all of the drugs and chemicals available to the American public, is cyclamate the only one dangerous enough to be banned?

STANLEY L. INHORN
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References and Notes

1. *Interim Report on Non-nutritive Sweeteners* (Food Protection Committee, National Academy of Sciences, Washington, D.C., November 1968).
2. J. M. Price, C. G. Biava, B. L. Oser, E. E. Vogin, J. Steinfeld, H. L. Ley, *Science* **167**, 1131 (1970).
3. W. C. Hueper, *Occupational and Environmental Cancers of the Urinary System* (Yale Univ. Press, New Haven, 1969).