Comment by J. Lederberg on the
Report of the Medical Advisory Group on Cyclamates

This is a reasonable and balanced report of the scientific background
to the decision by Secretary Finch (Oct. 18, 1969). The assertion that
"there is no evidence that cyclamate causes cancer in humans" that is often
quoted in connection with this administrative action has been the source of
great confusion, and will appear to be at odds with the recommendations of
the committee.

It would be equally correct to say "We do not know whether cyclamate
causes cancer in man, but have no affirmative reason to believe that man
will react differently from experimental animals." No studies have appeared
to date that can set an upper limit to the chronic risk of bladder cancer in
man from the consumption of cyclamates. They would be difficult to do. For
example, if the incidence of induced cancers were as low as one percent, it
might be almost impossible. However, it would be most desirable to conduct
long-term follow-ups in selected groups for which some control might be found;
for example, diabetics whose reports on nutritional history might be especially
credible, and who might be divided into habitual users and non-users of
cyclamates.

A plausible but alarming analogy might be drawn between cyclamate, or
its conversion product, cyclohexylamine and the industrial carcinogen,
2-naphthylamine (iv). Upwards of 20% of workers exposed to this dyestuff
chemical have had bladder cancer (Hueper, 1969), but repeated efforts to
produce cancer with it in experimental animals failed. Eventually they
succeeded, but this required chronic feeding of dogs for 3 years, an
experiment that has not been attempted with cyclamates. Then, successful
results were also obtained with the technique of implanting pellets
containing the chemical directly in the urinary bladder.

There is some evidence (Rodansky and Brill, 1970; see Miller and Miller,
1969) that the actual carcinogen is the -NHOH derivative, N-hydroxy,2-
naphthylamine (v). The corresponding -NHOH derivative, see iii below, has
also been reported (Goldberg et al.) as a metabolite of cyclohexylamine.

The conversion of cyclamate (i) to cyclohexylamine (ii) is not well
understood. However, some evidence has been published (Renwick and Williams,
1969) that this is accomplished by gut bacteria, and that chronic consumption
of cyclamate augments this capacity, presumably by encouraging the corresponding
micro-organisms.
The observation that synthetic sweeteners (saccharin, I could find no
reference to cyclamate) enhance appetite in satiated animals (Valenstein,
1967) has just begun to provoke more detailed behavioral studies. Stone et
al. (1969) reared rats on control vs. cyclamate-enriched diets. Their first
finding was that the cyclamat-rats showed some advantage in maze-learning
tests. However, this was then shown to be due to sustained hyperactivity
of the cyclamat rats, especially when deprived of food. These differences
were not reversed in the adult.

REFERENCES


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