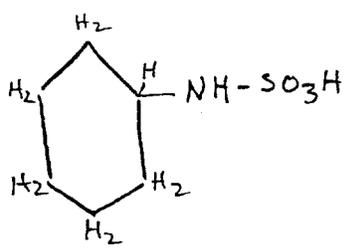
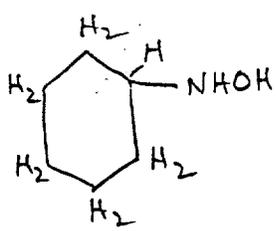


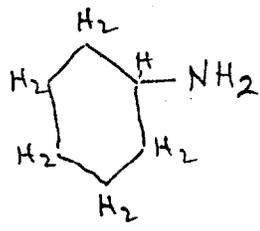
Comment by J. Lederberg on the Report of the Medical Advisory Group on Cyclamates Roger O. Egeberg et al., JAMA 211:1358-61 1970 (2/23).



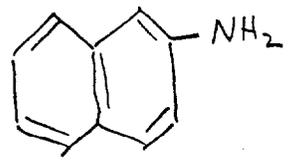
i) cyclamic acid



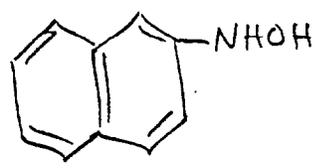
iii) N-hydroxy-cyclohexylamine



ii) cyclohexylamine



iv) 2-naphthylamine



v) N-hydroxy-2-naphthylamine

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.

See esp. *

2.

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 cyclamate-rats showed some advantage in maze-learning tests. However, this was then shown to be due to sustained hyperactivity of the cyclamate rats, especially when deprived of food. These differences were not reversed in the adult.

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