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Possible Hazard from Cyclamates in Diet Foods

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"Contains ----- cyclamate, a non-nutritive artificial sweetener which should be used only by persons who must restrict their intake of ordinary sweets."

1. Summary

The label shown above can be found in small print on packaged foods which contain cyclamate, an artificial sweetener (20). Most consumers do not worry about hazards of eating artificial sweeteners which are sold without restrictions. The R.C.S.I. cautions consumers that cyclamates may be hazardous to humans, and that the hazards remain to be adequately evaluated. We recommend that consumers heed the warning label and limit the amount of cyclamate in their diets to medically established needs.

2. How was Cyclamate Cleared for Use?

The sweetening properties of cyclamate were described in 1944 (5). Later, Abbott Laboratories put cyclamate through a series of safety tests (1, 2, 4), submitted the results to the U. S. Food and Drug Administration (FDA) and requested permission to market cyclamate as an artificial sweetener. This procedure is prescribed by law for all new food additives. FDA scientists carried out additional tests (3).

The results of these safety tests are summarized in Table I. They led to the conclusion that cyclamate by itself had no toxic effects on humans when eaten in small amounts and that adults could take up to five grams daily without fear of damage ascribable to cyclamate.

There is always the possibility, however, that a relatively harmless compound will be altered by the body into a more harmful compound. One method to determine if such a change is occurring is to determine the fraction of an administered dose which can be recovered. Such dose recoveries are done on excreta (excretion tests) and the organs and tissues (distribution tests). The distribution and excretion tests for cyclamate on which the license was based are also summarized in Table I.

The first tests were done on rats. In the short run, cyclamate accumulated to the greatest degree in liver and kidney, and only slightly in brain and other tissues; in general, most of it appeared to be excreted unchanged in the urine and feces (78-106% of a single injection was recovered in 2-4 days) (2). In tests on

people, cyclamate was also excreted in the urine and feces but the results were not uniform. After an intravenous injection of 1 gram of cyclamate to 5 subjects, four had excreted from 84% to 98% in the urine while one had excreted only 36% (urine was collected for 72 hours in each case). After eating 5 gm/day of cyclamate for an extended period, an average of 37% of the daily dose appeared in 24-hour urine samples (the rest may not have been absorbed from the intestine, may have been absorbed and excreted in the feces, or may have been excreted after the study was completed) (4). The FDA accepted the working assumption that cyclamate was excreted leaving no significant amount to be transformed or accumulated in the body.

At this point, the regulatory agency (FDA) asked an impartial scientific committee to further check the safety of cyclamate. The study was done by a committee of the National Academy of Science - National Research Council. This group of experts had access to unpublished records of research in the FDA files (most of this material presumably was used in the publications shown in Table I). The FDA apparently followed the recommendations of the committee in licensing cyclamate as a food additive.

3. What was Wrong with the Tests?

The published reports of investigations used in licensing cyclamate as a food additive are summarized in Table I. The R.C.S.I. finds that some important areas of investigation were not reported in the publications. Moreover, certain doubts arise directly from the reports.

1. The recovery tests were inconclusive. There was no FDA-approved method for measuring cyclamate in any biological material (the only accepted method was for measuring cyclamate in soft drinks (8, 9, 10)). Even with existing tests, recovery values had a wide range (4). This suggests: (a) the analytical methods were inadequate; (b) the experimental designs were inadequate; or (c) cyclamate is stored in the body or altered to some compound which would not be recognized in tests for cyclamate.

2. The recommended limit of daily intake did not acknowledge the standard rule of prudence for food additives which would have required that a 10-fold margin of safety be met (6). That is, the maximum amount of cyclamate ingested should be no more than one-tenth of the amount which produced the first undesirable effect. Since eating 5 grams of cyclamate per day results in changes in the stool (4), the recommended limit, ideally, should have been 0.5 grams daily. Actually, it was set at 5 grams daily.

3. Adequate tests of carcinogenic (cancer-producing) actions or teratogenic (embryo-damaging) actions are missing from the literature. Cyclamate was known, however, to penetrate readily into the fetus (2).

4. Since cyclamate has been distributed in diet foods, its effects on the population have been checked only through routine medical reports of adverse reactions. No large-scale epidemiological studies have been published (cyclamate has not been checked as fluoride, for example, was checked).

TABLE I

Evidence for Licensing Cyclamate as a Food Additive

Results of studies of cyclamate published in 1951-1953 are in this Table.

Results of later studies are in the text, Sections 4 and 5.

Kind of Test and Reference	Dose and Duration of Test	Results
1. Tests for Toxicity		
Amount given by mouth that killed half of the tested mice or rats (1)	10 to 12 gm/kg body weight (4.5 to 5.4 gm/pound); death occurred in 1 to 24 hours	Fluid accumulation in intestine; heart slightly distended
Physiologic changes in animals (metabolic rate, smooth muscle, heart muscle) (1)	1 injection; up to 0.5 gm/kg	None directly attributed to cyclamate
Pathological changes in organs of dogs and rats (1)	21 days (rats) and 30 days (dogs); up to 4 gm/kg daily by mouth	None directly attributed to cyclamate
Changes in nitrogen balance of two men eating cyclamate (4)	18 days; 5 gm/day	None
Changes in calcium and phosphate balances of two men eating cyclamate (4)	18 days; 5 gm/day	Positive balances ascribed to the calcium content of the cyclamate
Only adverse effects of cyclamate (4)	7½ months; 5 gm/day orally	Loose stools
Growth, food intake, mortality and pathology of rats (3)	24 months; 1% or less in diet	None directly attributed to cyclamate
Characteristics of litters of 3 generations (1)	30 months; 0.05% cyclamate in diet	"Normal litters"

TABLE I (Cont'd.)

Kind of Test and Reference	Dose and Duration of Test	Results
2. Tests of Excretion and Distribution		
Distribution of S^{35}-cyclamate in rats (2)	1 injection of 0.1 gm/kg	Highest organ concentrations were in liver and kidney at 4 hours
Recovery of eaten S^{35}-cyclamate in excreta of rats (2)	5 days; 80-120 mg/kg/day	Average of 88% recovered after nine days
Recovery of eaten cyclamate in urine; one person (1)	1 feeding of 0.3 gm; urine collected for 1 week	79.5% recovered
Recovery of intravenously injected cyclamate in urine; five persons (4)	1 injection of 1 gm; urine collected for 72 hours	36% recovered in one subject; 84-98% recovered in four subjects
Average daily urinary excretion of daily dose taken by mouth	5 gm/day; 7½ months	Average 24-hour urinary recovery was 37% of daily dose

4. New Evidence of Potential Damage from Cyclamate and Official Recommendations.

While cyclamate became the most widely used artificial sweetener in the U.S., no more research was published on it for ten years. In 1967, J. S. Leahy (7) confirmed a Japanese report (11) that cyclamate was changed in the body of some people to another compound, cyclohexylamine (CHA). This revived the scientific interest in cyclamate. Results of subsequent research led the FDA to ask for a new scientific evaluation of the safety of cyclamate and this was undertaken by a committee of the NAS-NRC (22). Here is the new evidence the members on that committee had to consider.

> Cyclohexylamine (CHA) is at least twenty times more toxic, acutely, than its relatively harmless parent, cyclamate. CHA killed 50% of a tested population of rats at doses of 0.3 gm/kg body weight when given by mouth, and it produced microscopic changes (granular degeneration) in livers and kidneys of rats at 0.06 gm/kg body weight, which is 28 mg/pound (19). Some persons who eat cyclamate convert it to CHA in their bodies. There are "high converters", who can transform large proportions of a cyclamate dose to CHA (values up to 40% have been reported); others transform it to a slight extent, while some persons apparently do not transform it at all (17). CHA, in turn, may not be removed from the body as fast as cyclamate. One person eating cyclamate, 1 gm/day for 17 days, apparently had more CHA in his body with each passing day (14).

The committee had access to unpublished records and its report to the FDA was not open to the public. The official conclusion was that there was no serious hazard of toxicity from cyclamate. However, it was also concluded that the quantity of cyclamate in diet foods should be stated on the label in milligrams and that the label should also warn that adults should not take more than 3.5 gm daily and children should not take more than 1.2 gm daily. These limits are reductions of previous limits (22).

In theory, diet foods should be so formulated as to keep the amount of cyclamate people eat under the limits recommended by the FDA. We have prepared a list showing the amounts of cyclamate in diet foods. This list, the R.C.S.I. Bulletin #2 on Food Additives, shows, for example, that three or four bottles of popular diet soft drinks have enough cyclamate to exceed the recommended daily limit for children.

5. Latest Information about CHA and R.C.S.I. Recommendations.

A disturbing scientific finding was made so recently that it appeared only as a preliminary report and, consequently, was not used by the scientific committee that made the recent decision on the safety of cyclamate. A team of FDA scientists found adverse effects of CHA on chromosomes, the carriers of heredity in cells. In male rats, a single injection of 10 mg or more per kg of body weight caused breaks in chromosomes of germ cells and bone marrow cells (18). As a breaker of chromosomes, CHA becomes suspect of producing three kinds of delayed harmful effects. Chromosome breakers may be mutagens (producers of mutants), teratogens (producers of congenital damage) and carcinogens (producers of cancer) (18). Research on the hazards is now in progress, both in rats and men.

What is to be done meanwhile about cyclamate in diet foods? The FDA has the task of weighing possible hazards of a food additive against the damages caused by prematurely alarming the public and against losses to business. At this time, there is no convincing evidence that a ban on cyclamate is necessary.

> Two studies have been reported which looked for chromosome breakage in human cells. In one study (18), volunteers ate cyclamate and the incidence of chromosome breaks in white blood cells was measured for converters and non-converters to CHA. No changes from normal values were seen. The second study (21) showed that cyclamate added to cultures of human skin cells, white blood cells and cancer cells doubled or tripled the occurrence of chromosome breaks when compared with cultures to which no cyclamate had been added. The R.C.S.I. learned that more extensive studies of chromosome breakage by CHA in both men and rats are now in progress. The long-term effects of CHA have not been published.
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> It remains to be established whether humans react to CHA as rats do and if the resulting damage to chromosomes, if any, has long-term harmful consequences to health and heredity.

Faced with these considerations, the FDA decided, for the present, to press studies of chromosome damage and leave cyclamate on the market.

The individual consumer does not need to give cyclamate the benefit of the doubt. Today cyclamate is suspected of causing genetic damage. The suspicion is scientifically sound, the hazard may be serious, and other ways of dieting are available. The R.C.S.I. suggests that, for the present, you heed the warning label and take cyclamate-containing foods only if ordered to do so by a physician.

For those who enjoy cyclamate-containing foods and choose to continue to eat them, R.C.S.I. Bulletin #2 on Food Additives provides a guide for keeping the daily intake below the limits set by the FDA.

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