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## Looking Back: Cyclamate

### **Cover Page Footnote**

Based on work under National Science Foundation Grant SBR-9808684 to Allan Mazur for the re-evaluation of public warnings raised during the 1950s and 60s about ostensible hazards to health or the environment. Nothing expressed here necessarily reflects the views of the NSF

# Looking Back: Cyclamate\*

Allan Mazur & Kevin Jacobson\*\*

## Introduction

Cyclamates are a class of synthetic, non-caloric sugar substitutes, not as sweet as, but without the unpleasant aftertaste of, saccharin. First approved in 1950 for use by diabetics and severely obese people, the Food and Drug Administration (FDA) in 1958 reclassified them as acceptable food additives, based on a rather short history of apparently safe use. Then the American image of feminine beauty was busty and hippy, but, during the 1960s, as slender figures became the ideal, the market increased for diet foods, especially sodas; use grew rapidly until cyclamate was consumed by three-quarters of Americans.<sup>1</sup>

The 1960s were also a time of increasing public concern about chemical adulteration of food and water. The battle against microbe adulteration had largely been won in the early decades of the century, and scarcity was the major food concern during the Depression and World War II. In the bountiful 1950s we were warned to vary our diet so that we would get all necessary nutrients, as when television's popular science teacher, "Mr. Wizard," advised us incessantly to start each day with a "better breakfast" of fruitcereal**milkbreadandbutterwitheggs-orbreakfastmeatforvariety**. No concern here with fat or cholesterol, much less chemical additives or pollutants. We bought DDT "bugbombs" to destroy insects in homes and gardens, while trucks and airplanes sprayed clouds of that inexpensive insecticide over fields and neighborhoods, often far more than recommended, carelessly engulfing animals and people. Most people didn't care then.

\* Based on work under National Science Foundation Grant SBR-9808684 to Allan Mazur for the re-evaluation of public warnings raised during the 1950s and 60s about ostensible hazards to health or the environment. Nothing expressed here necessarily reflects the views of the NSF.

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<sup>1</sup> Edward Lawless, *Technology and Social Shock* (1977); Allan Mazur, *U.S. Trends in Feminine Beauty and Overadaptation*, 22 *J. Sex Res.* 281 (1986).

By the late 1950s, Americans on the political left were complaining of the hazard of trace doses of radioactivity from the atmospheric testing of atomic bombs. At nearly the same time, but on the political right, was a mass protest against adding fluoride — toxic in high doses — to public water supplies at one part per million to prevent dental cavities. Despite little overlap in memberships of these movements, the arguments were basically the same. In 1958 a clause introduced by antifluoridationist U.S. Representative James Delaney forbade the FDA from approving as, e.g. a food additive, any chemical that causes cancer in man or animal.<sup>2</sup> These political movements paved the way for Rachel Carson's best-seller, *Silent Spring*, warning of trace pesticides. It appeared in 1962, just as the tranquilizer thalidomide was announced to cause birth defects when taken by pregnant women. Approved for use in Europe but not here, thalidomide had caused babies to be born with flipper-like stumps instead of arms and legs. Dr. Frances Kelsey of the FDA had single-handedly stood firm against great pressure and abuse in denying its approval, thus saving America from tragedy. She provided the best press the FDA ever had.<sup>3</sup>

Cyclamate was among several food additives and drugs that became suspect during the 1960s.<sup>4</sup> The National Academy of Sciences, in periodic reviews for the FDA of cyclamate toxicity, found the sweetener generally safe but warned against uncontrolled public distribution because of physiological effects including diarrhea, and the unknown consequences of prolonged exposure. Also, doubts were raised that people using cyclamates actually lose weight. In 1968 FDA scientists led by Dr. Marvin Legator showed that cyclohexylamine, a metabolite of cyclamate that forms in the digestive tract, causes chromosome breakage in rats, suggesting the possibility of gene damage. Responding to these concerns in December 1968, the FDA reduced its recommended daily upper limit for cyclamate to 50 milligrams per kilogram of body weight, which meant that two cans of diet soda might exceed the limit for a 60-pound child.

In the meantime, another FDA scientist, Dr. Jacqueline Verrett, had been injecting cyclamate into chicken eggs, producing embryo

<sup>2</sup> See *Public Citizen v. Young*, 831 F.2d 1108, n.1 (D.C. Cir. 1987).

<sup>3</sup> Allan Mazur, *Why Do We Worry About Trace Poisons?* 7 *Risk* 35 (1996).

<sup>4</sup> James Turner, *The Chemical Feast* (1970).

deformities. These results were forcefully brought to the attention of FDA Commissioner Herbert Ley in April 1969 when one of Verrett's superiors carried deformed chicken embryos into Ley's office, but the Commissioner took no action. On October 1, 1969, Dr. Verrett was interviewed on NBC television news, apparently with the consent of an FDA deputy commissioner. Setting off a wave of concern, she described her finding that cyclamate deforms chicken embryos, its thalidomide-like inference to human embryos fairly obvious. Verrett's appearance drew an immediate rebuttal from Commissioner Ley, saying "Cyclamates are safe within the present state of knowledge and scientific opinion available to me." Spokesmen for Abbott Laboratories, one of the largest cyclamate producers, also declared the sweetener safe and attributed the alarm to the sugar industry.<sup>5</sup> Commissioner Ley's boss, Secretary of Health, Education and Welfare, Robert Finch, was drawn into the controversy, criticizing in the press FDA's handling of safety questions about cyclamate and indicating that reorganization of the agency's procedures and personnel was inevitable.

Two weeks later, Abbott Laboratories released a study it had commissioned showing that 8 out of 80 rats fed large amounts of a mixture of ten parts cyclamate to one part saccharin (proportions most often used in diet sodas) developed bladder tumors, some cancerous. This was the basis for Secretary Finch's announcement, at an October 18 press conference, that indications of cancer clearly placed cyclamate in violation of the Delaney Clause. Therefore the FDA could no longer allow it to be used in nonprescription drinks and foods, and products with cyclamate must be recalled from stores. The following year, 1970, the FDA banned cyclamate from prescription products too.

### Risk Assessment

It had not been cancer but the thalidomide-like birth defects in televised chick embryos that had spurred public concern over cyclamate in 1969. Today this is not an issue of scientific concern. Injection of a chemical into a chicken egg is devalued by authorities as a test for human birth defects because there is no parallel between the chicken embryo and a mammal's placenta. In any case, new feeding tests

<sup>5</sup> *Id.*; Morton Mintz, *Rise and Fall of Cyclamates*, *Washington Post*, Oct. 26, 1969, at A1.

showed that cyclamate does not produce birth defects in mammals.<sup>6</sup>

The FDA's judgement that cyclamate may cause bladder cancer was based on one study of rats fed a combination of cyclamate and saccharin. (Tests where cyclamate materials were implanted into rodent bladders were generally discounted because implantation does not correspond with feeding as a route of administration.) By 1982, when Abbott Labs and a trade organization, the Calorie Control Council, petitioned anew for approval of the sweetener, some twenty new cancer bioassays had been conducted in which cyclamate was fed to a variety of animals species without showing any cancer-causing effect, even at high doses. Two attempts to replicate the original study linking cyclamate to bladder cancer failed to produce cancer in rats. The cause of the tumors in the original rats was never established, but conjectured causes include parasites or stones in the rats' bladders, or environmental contamination of some of their cages.<sup>7</sup>

In 1984 the FDA's own Cancer Assessment Committee concluded that cyclamate is not carcinogenic. The Agency, under embarrassing pressure to reverse its ban, asked the prestigious National Academy of Sciences to evaluate the cancer causing potential of the sweetener. The Academy concluded the next year, on the basis of epidemiological and animal studies, that neither cyclamate nor its metabolite cyclohexylamine are carcinogenic. However the Academy did not fully exonerate cyclamate, instead suggesting more investigation of hints that it could be a co-carcinogen, promoting the action of other cancer-causing substances that might be in the body.<sup>8</sup>

While the cancer issue was moving toward resolution, the prospect of genetic damage remained ambiguous. Legator's 1968 finding, that the metabolite cyclohexylamine causes chromosome breakage in rats,

<sup>6</sup> M. Jacqueline Verrett, et al., *Toxicity and Teratogenicity of Food Additive Chemicals in the Developing Chicken Embryo*, 56 *Toxicol. & Appl. Pharm.* 273 (1980); Barbara Bopp, Robert Sonders & James Kesterson, *Toxicological Aspects of Cyclamate and Cyclohexylamine*, 16 *CRC Critical Reviews of Toxicology* 213 (1986); *Sweeteners: Health Effects* (Gary Williams, Ed. 1988).

<sup>7</sup> Calorie Control Council and Abbott Laboratories, *Food Additive Petition for Cyclamate*, 2A3672 (1982); Kathleen Meister, *Low-Calorie Sweeteners* (Amer. Council on Science and Health 1993).

<sup>8</sup> National Academy of Sciences, *Evaluation of Cyclamate for Carcinogenicity* (1985). The same conclusion had been reached by the FDA's Cancer Assessment Committee a year earlier.

could not be confirmed by other investigators. Many other tests were run using diverse methods; some supported the possibility of gene damage, some did not. This matter was complicated by great uncertainty, still not fully resolved, about how to test for mutagenic effects. Scientists associated with Abbott or sponsored by the Calorie Control Council, evaluating the entire battery of tests, concluded that neither cyclamate nor its metabolite represent a significant mutagenic hazard.<sup>9</sup> We are not aware of a serious challenge to their conclusion, but the issue may never be fully resolved.

Nothing can be proven 100% safe. By 1989, cyclamate seemed to have sufficiently passed muster. The front page of the Washington Post claimed the FDA was

widely expected to reapprove it, possibly this year. Once accused of causing everything from bladder cancer to birth defects, cyclamate is now widely thought to be harmless.

The acting director for the FDA's Center for Food Safety and Applied Nutrition was quoted "saying that with cyclamate we made a mistake." Referring to a 1980 FDA refusal to lift the ban, back in 1980, he said, "The matter was taken out of the hands of the scientists here and handled by attorneys."<sup>10</sup>

Whether because of its attorneys or scientists, the FDA did not reapprove cyclamate in 1989 nor has it acted on the petition as of this writing, ten years later. New suspicions had arisen about cyclamate's metabolite. Male animals show testicular atrophy when fed cyclohexylamine at high doses. The petitioners responded that there would be no diminution of testicles if the acceptable daily dose of cyclamate were suitably low. Also, the FDA was concerned that the metabolite elevated blood pressure in test animals and humans, leading to a new round of research.

### Conclusion

The diet soda industry, representing about 60% of cyclamate use, quickly responded by substituting a saccharin-sugar mixture, and

<sup>9</sup> Bopp, et al., *supra* note 5, at 276; see also Brusick et al., Assessment of the Genotoxicity of Calcium Cyclamate and Cyclohexylamine, 14 *Env'tl & Molecular Mutagenesis* 188 (1989).

<sup>10</sup> Malcolm Gladwell, *U.S. Expected to Lift Ban on Cyclamate*, Washington Post, May 16 1989 (quoting Robert Scheuplein).

consumption of diet products continued upward. Industry criticized the Delaney Clause as too restrictive, preventing any balancing of benefits and risks of additives, but it remains in effect. Then, the FDA in 1977 proposed to ban saccharin too when animal research suggested that it caused bladder cancer. However, Congress quickly set the ban aside. Today saccharin remains in use, along with the newer aspartame and the newest non-caloric sweetener, acesulfame potassium.

Cyclamate does not cause cancer or birth defects as once feared. Yet, as each suspected harm was ruled out, others surfaced, e.g., co-carcinogenicity, testicular atrophy and high blood pressure. For defenders, this resembles the carnival game, Whack-A-Mole; as moles are beaten back into their holes, others emerge. For critics, it resembles a pearl-rich bed of oysters; if enough are opened, a pearl may appear: There will always be more to open until assessors lose interest, as may be happening.

More than 50 nations, including most of Europe, approve cyclamate. The World Health Organization's Joint Expert Committee on Food Additives has consistently found cyclamate safe. Canada, in a twist from the U.S. position, has more stringent restrictions on saccharin than on cyclamate, allowing both as table-top sweeteners but only cyclamate to sweeten drugs. Sweden, another nation with a cyclamate ban, was told by the European Commission in 1999 that European Union law forbids that because cyclamate is not harmful.<sup>11</sup>

The petition for approval of cyclamate that Abbott Labs and the Calorie Control Council submitted to the FDA in 1982 is still pending. The FDA will not comment on pending petitions, so we do not know if it is under active consideration. Abbott says it is no longer interested, but a spokesperson for the Calorie Control Council tells us that some companies still want to use it. Given considerable public suspicion about chemical sweeteners, probably including several now awaiting approval, the industry would no doubt enjoy seeing cyclamate's reputation restored, even if it never appears in U.S. markets.



<sup>11</sup> Reuters, *EU Rejects Swedish Restrictions on Food Additives*, Jan. 8, 1999.