THE LAST WORD SOCIETY

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Dulcin: A Centennial Perspective

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ABSTRACT: The discovery of dulcin, the second synthetic sweetener, has been traced to the work of J. Berlinerblau. Early studies of this sweetener revealed a very effective sweetener that showed toxicity at high doses. Dulcin never achieved great recognition nor usage but was utilized slightly until a long-term study clearly pointed out its toxicity under sustained use with small doses.

KEYWORDS: toxicology, Last Word Society, dulcin, sweetener, toxicity

A new drug made its appearance about 100 years ago. It was dulcin (Fig. 1), the second synthetic sweetener, and it was in use for nearly 70 years until questions of its toxicity were finally clarified. Why should scientists be concerned about dulcin? It was not only the second synthetic sweetener since it was discovered only five years after saccharin (Fig. 2), but was the first synthetic sweetener about which serious questions of toxicity arose. Also, it was chemically unrelated to saccharin; the first demonstration of the fact that synthetic sweeteners have generally been chemically distinct from each other. Dulcin possessed a sweet taste and did not exhibit the bitter aftertaste of saccharin, helping scientists to realize the interplay of these two taste sensations. For these reasons, a brief examination of the history and development of this material seems quite appropriate.

The discovery of dulcin has not been addressed in the literature. It has been stated that nothing is known of its discovery. Saccharin's discovery was reported in 1879 by Ira Remson and Constantine Fahlberg. News of this discovery had brought the idea of a synthetic sweetener into awareness, but there is no evidence nor any reason to believe that this event had any influence upon the discovery of dulcin. The credit for the discovery of the sweet taste of this material must be granted to Dr. Joseph Berlinerblau. He was originally from Warsaw and this work was done as part of his doctoral dissertation for Bern and was published in 1884. The work was done in the laboratories of a Dr. Schmitt in Dresden. His intent was to study the effect of chlorine cyanide on various aromatic amines, a reaction previously explored by others with ammonia and several simple amines. When *para*-phenetidine was treated with chlorine cyanide, it formed an intermediate *para*-ethoxyphenylcyanamide, which, upon absorption of water, was converted into *p*-ethoxyphenylurea or *p*-phenetolcarbamide; he synthesized this compound also by mixing the acid salt of *p*-amidophenetole with a solution of

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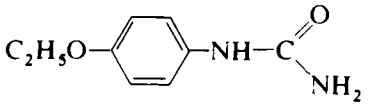

FIG. 1—*Chemical composition of dulcin.*

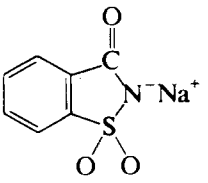

FIG. 2—*Chemical composition of saccharin.*

potassium cyanate [*1,2*]. Dr. Berlinerblau proceeded as he did with all compounds prepared in this study to describe its physical properties. He clearly states in this section that this *p*-ethoxyphenylurea has a very sweet taste [*1,2*]. It does appear that, in the course of handling this compound, its sweet properties became known. The exact details of how this happened are still not clear.

In 1891, Dr. Berlinerblau secured a patent for a new synthetic approach treating *p*-phenetidine with phosgene to form an intermediate which was quickly converted to the sweetener by the addition of ammonia [*3*]. Other synthetic procedures were developed thereafter by a variety of chemists.

The first use of the term dulcin appears in the literature in 1893 by Kossel. Kossel conducted a series of experiments on dogs and rabbits and found no detrimental effect on either when a daily dose of 2 g (30 grains) was given for 25 days [*4*]. He considered appetite, weight, respiration, circulation, and the central nervous system in this work. Very large doses (4 g) did induce some toxicity and the dogs died with some evidence of blood destruction. Kossel estimated that dulcin was 200 times as sweet as cane sugar. Kobert believed that dulcin would be perfectly safe as long as very large doses were avoided [*5*]. Dr. Ewald gave the drug in doses about 1.5 g daily to patients and claimed it was safe at this moderate level [*6*]. He praised its taste as being superior to saccharin since it had no bitter aftertaste and indicated it was especially valuable for diabetics. Tablets containing 0.4 grain of dulcin could be used by such patients as their sweetening agent. In opposition to these claims of safety, Aldehoff found that daily doses of only 1 g (15 grains) were harmful and that in a few weeks this level was fatal to the dogs which died with symptoms of acute jaundice [*7*]. Thus, the few early tests performed with dulcin gave mixed reviews on its safety while praising its taste, and the question of its toxicity appeared to be potentially serious.

After this initial interest, a survey of the literature for any mention or description of dulcin yielded only a few sources. It is mentioned only briefly or sporadically or both. It is very briefly noted in the 1894 *National Dispensory*, the 1896 *Merck's Manual*, Richter's *Organic Chemistry*, and Straub's *Lehrbuch der Pharmakologie* (1934). A very short description appears in Samuel Sadtler's *Pharmacetical and Medical Chemistry* (1895), Moeller and Thomas's *Real Enzyklopadie der Gesamten Pharmazie* (1905), the 1899 and the 1906 editions of Shoemaker's *Materia Medica and Therapeutics*, and the 1908 and 1909 editions of Potter's *Therapeutus Materia Medica and Pharmacy*. It is mentioned in Lynn's first edition of *Phar-*

maceutical Therapeutics (1929) within the section on substances of no direct remedial value and described only as being sometimes encountered; it is not mentioned at all in the second edition (1938) even though saccharin was included in both editions. It is given a one sentence identification in the 4th (1938) and the 5th (1947) editions of Bastedo's *Materia Medica* while it was not present in the 2nd (1918) or the 3rd (1933) editions. In Remington's *Practice of Pharmacy* editions from 1894 to 1948, it is described only as a new sweetening agent listed under the Glossery of Uncommon Names section of the book. Only Shoemaker's works even mention potential toxicity. Note that while great attention was being given to saccharin, dulcin appears to have been relegated to a very distant second. The very small amount of information provided was neither really informative nor helpful in judging dulcin's value or toxicity. Nor does the data suggest that dulcin was used to any great degree.

Additional studies on dulcin after the original set of studies were slow in coming. There were two studies indicating that large doses of dulcin could be toxic. One of these dealt with a poisoning case involving Dulcin. Another author suggested that dulcin may have an accumulative effect but no data suggested what damage could come from small repeated doses. A two-year feeding study on rats examining the chronic toxicities of saccharin, dulcin, a newly discovered cyclamate, and a fourth proposed sweetener was carried out by representatives of the Division of Pharmacology, Food and Drug Administration. They found that dulcin exhibited toxic effects at 0.5% including anemia, lowered growth rate, mortality rate increases and other problems, and even at 0.1% where liver adenomas were found as well as splenic enlargement and darkening associated with chronic congestion, pulp hyperplasia, and increased hemosiderin content [*8*]. They concluded that because of the extensive damage noted in their experiments, dulcin could not be considered safe for food or drug use even in small quantities. After this report, dulcin seems to have been discounted and references to it vanished nearly completely.

Because of the lack of information, there is much we shall never know about dulcin. Were there other poisoning cases besides the one reported? Were there unpublished studies that could have helped in our understanding at an earlier period? Dulcin never really became popular or widely used, but considering its toxicity, that was probably a good thing. By the time that dulcin began to be studied, saccharin was becoming the established sweetener. One can only speculate as to what might have happened if dulcin had been discovered a few years earlier to make it the first sweetener. There are lessons here worth considering as future sweeteners are proposed.

Conclusion

The second synthetic sweetener, dulcin, was discovered in 1884 by J. Berlinerblau. Early testing did not yield definitive results regarding toxicity. The sweetener gained only limited acceptance and gradually disappeared from the market after an unfavorable comprehensive long-term toxicity study was published in 1951. Nevertheless, dulcin did provide some useful insights into the chemistry of sweetness.

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