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FDA's approval of **aspartame** under scrutiny

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The Globe and Mail

A revolutionary low-calorie sweetener has brought stellar fortunes to its U.S. manufacturer, but critics say it should never have been approved.

NutraSweet, a household word in more than 50 countries, is a brand name for **aspartame**, the sweetener sold by NutraSweet Co. of Skokie, Ill. Last year, the company had record revenue of \$711-million (U.S.).

But documents released by U.S. Senator Howard Metzenbaum (D, Ohio) and by Adrian Gross, a scientist formerly with the U.S. Food and Drug Administration, reveal serious irregularities in the FDA's approval of **aspartame**.

The senator's office is conducting an investigation. A date will soon be set for a Senate hearing on **aspartame**-related health concerns, a staff member said.

The convoluted sequence of botched laboratory tests, squelched grand jury investigations, and revolving-door relationships between government and industry employees, began in 1965, when a pharmaceutical company, G. D. Searle & Co. of Skokie, accidentally discovered the sweetener.

In 1970, the company obtained a patent for **aspartame**. Later that year, an internal memo urged company management to get FDA officials into the "habit of saying yes" and to foster in them a "subconscious spirit of participation."

In 1974, the FDA approved **aspartame's** commercial use, over objections by one of its scientists. But lawyer James Turner and medical researcher John Olney immediately filed a complaint that floored Searle's marketing plans.

Dr. Olney had found an elevated incidence of brain tumors in **aspartame**-fed rats. He also argued that **aspartame** and monosodium glutamate could together cause brain damage in children.

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Seven years later, the FDA ruled that **aspartame** would not cause brain damage or cancer in humans, but both issues are still debated.

Dr. Olney has described the FDA's approval of **aspartame** as arbitrary and irresponsible. Anthony Miller, formerly of the National Cancer Institute of Canada, said concerns that the sweetener may cause brain tumors and neurological damage have not been laid to rest.

The FDA said Dr. Olney's study showed human consumers would risk cancer only by ingesting impossibly large amounts of the chemical. Arthur Hayes, FDA commissioner in 1981, added that Searle's tests failed to support Dr. Olney's findings.

But Dr. Gross reviewed Searle's data and concluded that one test "established beyond any reasonable doubt that **aspartame** is capable of inducing brain tumors in experimental animals."

In another test, rats fed normal diets developed cancer at the same rate as rats given an **aspartame** breakdown product, but Dr. Olney and Dr. Gross said the tumor incidence in both groups was abnormally high.

A 1980 Public Board of Inquiry described the result as "bizarre," but the FDA turned down requests for more studies, claiming Dr. Olney had overestimated the natural incidence of brain tumors in laboratory rats.

Dr. Gross pointed out that Dr. Olney's calculations were based on a huge sample of almost 60,000 rats.

In a 1985 letter to Mr. Metzenbaum's legislative assistant, Dr. Gross asserted the FDA could not legally disregard Dr. Olney's findings.

U.S. law requires any company proposing a new food additive to prove that it does not cause cancer. There is no comparable law in Canada.

Another setback for Searle occurred when an FDA scientist noticed discrepancies in a test report on a drug the company was developing. Follow-up investigations led to an investigation of Searle's laboratory operations.

In 1975, FDA commissioner Alexander Schmidt appointed a special task force to examine 25 Searle tests, including 11 on **aspartame**. It discovered major shortcomings.

"We have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high-quality animal research to accurately determine or characterize the toxic potential of its products," the investigators wrote in their final report.

In July, 1976, Dr. Schmidt testified at a U.S. Senate hearing that he agreed with the task force's conclusions. In 1977, the FDA appointed a second task force that re-examined three of Searle's **aspartame** tests.

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The investigators found Searle had removed possible tumors from experimental animals, had failed to report all tumors discovered, had written experimental protocols partway through tests, had failed to test the stability of **aspartame** and other test substances, had possibly allowed animals to avoid eating test substances, and had made recording errors showing "dead" animals returning to life.

A Searle pathologist questioned on a key **aspartame** study told investigators: "You should have seen things when this study was run - there were five studies being run at one time - things were a mess."

In January, 1977, the FDA's chief counsel, Richard Merrill, submitted a 33-page letter to U.S. Attorney Samuel Skinner requesting a grand jury investigation of Searle's apparent violations of U.S. federal laws.

He suggested the poor laboratory practices may have been deliberate policy, "calculated by Searle to minimize discovery of toxicity and/or to allay FDA concern."

The Justice Department's investigation dragged on for almost two years. During that time, Mr. Skinner and another lawyer resigned from the case, and later accepted employment with the law firm defending Searle.

Mr. Skinner's resignation occurred when only six months remained of a five-year statute of limitations on the controversial tests. The investigation languished until a new U.S. Attorney, Thomas Sullivan, took office four months later.

By the end of 1978, Mr. Sullivan had dropped the probe, for reasons that have never been made public.

In May, 1985, Mr. Metzenbaum told Congress that Dan Reidy of the U.S. Attorney's office could not provide any answers, being bound by a law of secrecy regarding grand jury investigations.

A Searle spokesman contended the charges of wrongdoing were groundless, and that the grand jury had exonerated the company.

Former FDA commissioner Dr. Schmidt said he thought the charges were dropped because of insufficient evidence. "It's hard to bring a criminal indictment on the basis of sloppiness," he remarked.

The FDA next asked a team of university pathologists to evaluate 12 of Searle's **aspartame** studies, to determine if the tests had been done, and whether Searle had lied about the data.

The team found no evidence of fraud. However, the question of whether Searle's tests were valid remained open, because the scientists had been told not to evaluate experimental designs.

Nevertheless, the FDA did not order Searle to repeat any tests - a decision that Mr. Turner and Dr. Olney vigorously opposed.

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The FDA told the pair to save their concerns for a Public Board of Inquiry. But the 1980 board did not permit them to air their views.

After the board presented its report, Mr. Turner appealed to FDA commissioner Jere Goyan. "The entire argument that since the studies are no longer considered fraudulent by FDA, they are therefore scientifically valid is an example of a rhetorical shell game that, if successful, can only bring discredit and ridicule on the FDA," he wrote.

Walle Nauta, who had headed the board, also worried about the validity of Searle's tests. "There was considerable concern. It was a shocking story we were told," he said in a 1984 interview with Common Cause Magazine.

But Dr. Nauta had felt the board could not pursue the matter. "We had absolutely no way of knowing who was right. We had to take the FDA's word," he explained. The board therefore ruled that **aspartame** would not cause brain damage or interfere with hormones secreted in the brain.

It also concluded there were too many unresolved questions about brain tumors. This was disputed by the FDA Bureau of Foods, which said **aspartame** was safe and should be approved.

FDA commissioner Dr. Goyan could not make up his mind, and left office the following spring without handing down a decision.

Dr. Hayes was appointed commissioner in April, 1981. In July, he approved **aspartame** for use as a tabletop sweetener, despite dissent from three FDA scientists.

Mr. Turner continued to spar with the FDA. In 1983, he presented fresh evidence to the appeals court, suggesting **aspartame** may cause brain damage and eye damage.

FDA officials said they were unable to obtain research data from Richard Wurtman of the Massachusetts Institute of Technology on experiments purportedly linking **aspartame** to brain damage. They also said 130 complaints of impaired vision and blindness among **aspartame** users were "anecdotal."

Mr. Turner is now requesting a court order to acquire Dr. Wurtman's data.

In 1985, Mr. Metzenbaum asked the U.S. General Accounting Office to investigate six FDA employees, including Dr. Hayes and former Bureau of Foods acting director Howard Roberts, for possible conflicts of interest over **aspartame**.

The GAO could not prove the allegations, but noted that three out of five men interviewed refused to supply copies of their communications with FDA after leaving the agency.

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Mr. Hayes became senior scientific consultant to the company conducting Searle's public relations. Dr. Roberts became a vice-president of the U.S. National Soft Drink Association.

The FDA has approved **aspartame** for use in more than 100 products. Last November, refrigerated juice drinks and frozen confections were added to the list.

In Canada, Beverley Huston of the federal Government's Health Protection Branch said new uses of **aspartame** in products such as chocolate milk and ice cream will probably not be allowed until further studies have been completed.

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