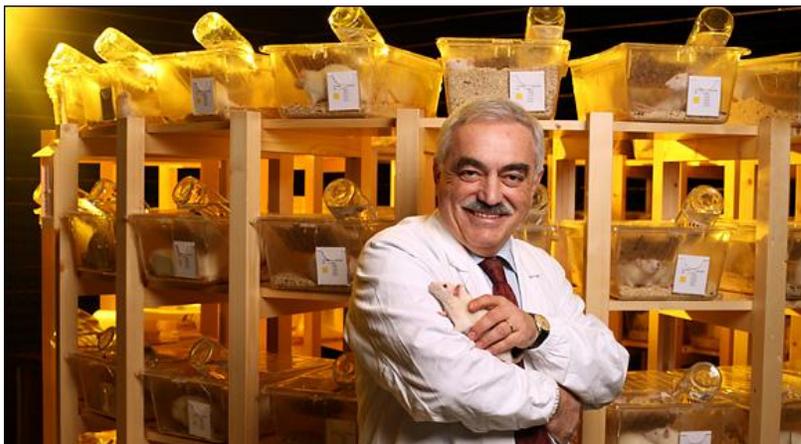


# Business

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## The Lowdown on Sweet?



Pigi Cipelli for The New York Times

Dr. Morando Soffritti, who led tests of aspartame on 1,900 rats, calls it a possible carcinogen.

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By **MELANIE WARNER**

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WHEN Dr. Morando Soffritti, a cancer researcher in Bologna, Italy, saw the results of his team's seven-year study on aspartame, he knew he was about to be injected into a bitter controversy over this sweetener, one of the most contentiously debated substances ever added to foods and beverages.

Aspartame is sold under the brand names Nutra-Sweet and Equal and is found in such popular products as Diet Coke, Diet Pepsi, Diet Snapple and Sugar Free Kool-Aid. Hundreds of millions of people consume it worldwide. And Dr. Soffritti's study concluded that aspartame may cause the dreaded "c" word: cancer.

The research found that the sweetener was associated with unusually high rates of lymphomas, leukemias and other cancers in rats that had been given doses of it starting at what would be equivalent to four to five 20-ounce bottles of diet soda a day for a 150-pound person. The study, which involved 1,900 laboratory rats and cost \$1 million, was conducted at the European Ramazzini Foundation of Oncology and Environmental Sciences, a nonprofit organization that studies cancer-causing substances; Dr. Soffritti is its scientific director.

The findings, first released last July, prompted a flurry of criticism from the Calorie Control Council, a trade group for makers of artificial sweeteners that has spent the last 25 years trying to quell fears about aspartame. It said Dr. Soffritti's study flew in the face of four earlier cancer studies that aspartame's creator, G. D. Searle &

Company, had underwritten and used to persuade the Food and Drug Administration to approve it for human consumption. "Aspartame has been safely consumed for more than a quarter of a century and is one of the most thoroughly studied food additives," read one news release from the council.

At the same time, Dr. Soffritti's findings have energized a vociferous group of researchers, health advocates and others who say they are convinced that aspartame is a toxin associated with a variety of health troubles, including headaches, dizziness, blindness and seizures.

DR. SOFFRITTI, who oversees 180 scientists and researchers in 30 countries who collaborate on toxin research, says that since last July, he has been contacted by some of these critics, including a member of Parliament in Britain and a number of conspiracy theorists, some of whom say they have suffered from "aspartame poisoning" and filled Web pages with cloak-and-dagger speculation about why the F.D.A. approved aspartame for sale a quarter-century ago.

No regulatory agency has yet acted on Dr. Soffritti's findings, although Roger Williams, a member of Parliament, called for a ban on aspartame in Britain last December. Last month, the European Food Safety Authority, an advisory body for the European Commission, began to review 900 pages of data from Dr. Soffritti; the goal is to finish by May. A commission spokesman, Philip Tod, said it was too early to know what the next steps would be if the scientists reviewing the data concurred with Dr. Soffritti's findings.

In the United States, the Food and Drug Administration says it has also taken note of the study, which is available online (<http://ehp.niehs.nih.gov/docs/2005/8711/abstract.html>) and is scheduled to be published next month in a medical journal financed by the National Institutes of Health. F.D.A. officials say that they, too, intend to conduct a thorough review.

But both the F.D.A. and the European Commission have cautioned that there is no need for people to avoid aspartame. "We don't see any concerns at this stage," said George H. Pauli, associate director for science policy in the F.D.A.'s Office of Food Additive Safety. "We've gone through a humongous amount of data on aspartame over the years."

Putting restrictions on aspartame would come at a significant cost. Food companies and consumers around the world bought about \$570 million worth of it last year. New regulatory action on aspartame would also jeopardize the billions of dollars worth of products sold with it. Already, in the United States, many companies are opting to use

sucralose, or Splenda, in their new low-calorie products, in part because it is less controversial.

Lance Collins, chief executive of Fuze Beverage in Englewood Cliffs, N.J., said that safety concerns about aspartame were a "major contributing factor" in his decision to use sucralose in his tea and juice drinks. Sucralose, however, is made by under a patent by just one company, Tate & Lyle of London, and is in desperately short supply.

Dr. Soffritti, who has spent 28 years doing research on potential carcinogens, said he was trying to steer clear of the growing political maelstrom. But he added that he was concerned about the large numbers of people who use aspartame, particularly children and pregnant women. "If something is a carcinogen in animals," he said, "then it should not be added to food, especially if there are so many people that are going to be consuming it."

Lyn Nabors, executive vice president of the Calorie Control Council, said Dr. Soffritti's study was not valid because the rats used in it had been allowed to live longer than the two-year standard established by the United States government's National Toxicology Program. "It's difficult to determine if the cancers you find are due to something else," Ms. Nabors said. "Just as in humans, the rat's body slows down later in life, and the aging process causes all kinds of things."

But John R. Bucher, deputy director of environmental toxicology at the National Toxicology Program, the government's agency for research on toxic chemicals, called the design of the Ramazzini study "impressive" and "thorough," and said that he did not think the fact that rats were allowed to live until their natural deaths had skewed the results.

Dr. Jose Russo, director of the breast cancer and environmental research center at the Fox Chase Cancer Center in Philadelphia, says that lifetime studies are "ideal" but that they are not done often, partly because they are more expensive than limited-time tests. Dr. Russo, however, criticized the Ramazzini study for not allowing outside pathologists to analyze all of the tissue samples where cancerous tumors were found. "People need to see every tumor," he said.

Dr. Bucher of the National Toxicology Program said pathologists at the program, with which Ramazzini collaborates, looked at 70 tumor slides. But with the study producing over 9,000 tumor-containing slides, James Swenberg, professor of environmental science at the University of North Carolina at Chapel Hill, says that this falls short of standard practice.

While Dr. Soffritti's methods have drawn some criticism, the Ramazzini cancer lab, which is financed by private bank foundations, governments and 17,000 individual members, has earned considerable credibility since it was founded in 1971 for its pioneering research on chemicals. It was the first research body to do studies showing that vinyl chloride and the gasoline additive methyl tertiary-butyl ether, or M.T.B.E., are carcinogenic, research that eventually encouraged the United States to strictly regulate vinyl chloride and that led 21 states to ban M.T.B.E.

Dr. Soffritti said he was inspired to look at aspartame because of what he calls "inadequacies" in the cancer studies done by Searle in the 1970's. He said that those studies did not involve large-enough numbers of rats and did not allow them to live long enough to develop cancer.

The Ramazzini study was conducted with 1,900 rats, as opposed to the 280 to 688 rodents used in Searle's studies, and the rats lived for up to three years instead of being sacrificed after two, which is the human equivalent of age 53. "Cancer is a disease of the third part of life," Dr. Soffritti said. "You have 75 percent of cancer diagnoses for people who are 55 years old or older. So if you truncate the experiments at 110 weeks and the rats are supposed to survive until 150 to 160 weeks, it means you avoid the development of cancer at the time when cancer would be starting to arise."

Others have also challenged Searle's studies. Documents from the F.D.A. and records from the Federal Register indicate that, in the years before the F.D.A. approved aspartame, the agency had serious concerns about the accuracy and credibility of Searle's aspartame studies. From 1977 to 1985 — during much of the approval process — Searle was headed by [Donald H. Rumsfeld](#), who is now the secretary of defense; Searle was acquired by Monsanto in 1985. Monsanto later spun Searle's assets out into two companies: Merisant, which owns the brands Equal and Canderel, and NutraSweet, which is owned by J. W. Childs Equity Partners, an investment firm in Boston.

A 1976 report from an F.D.A. task force, for example, found that Searle's studies on aspartame and several of the company's pharmaceutical drugs were "poorly conceived, carelessly executed, or inaccurately analyzed or reported." It cited what it called a lack of training by the scientists analyzing tissue samples, a "substantial" loss of information because of tissue decomposition and inadequate monitoring of feeding doses.

In response to the report, the F.D.A. asked the Justice Department to open a grand jury investigation into whether two of Searle's aspartame studies had been falsified or were incomplete. In a 33-page letter in 1977, Richard A. Merrill, the F.D.A.'s chief

counsel at the time, recommended to Samuel K. Skinner, then the United States attorney for the Northern District of Illinois, that a grand jury investigate the company, which was based in the Chicago suburb of Skokie, for "concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Aldactone and the food additive aspartame."

A grand jury was never convened, however. Shortly after the letter was sent, Mr. Skinner left the Justice Department to join Sidley & Austin, a law firm that represented Searle. After 12 years at that firm, now Sidley, Austin, Brown & Wood, Mr. Skinner was appointed to be President [George H. W. Bush's](#) transportation secretary; later he became his chief of staff. In 1978, a year and half after Mr. Skinner left the United States attorney's office in Chicago, his deputy, William F. Conlon, also left to work at Sidley & Austin.

Mr. Skinner, now a lawyer at Greenberg Traurig LLP, said that as soon as he began looking for a new job and interviewing with Sidley & Austin, he recused himself from the Searle investigation. Mr. Conlon, who is still at Sidley & Austin, did not return phone calls.

Over the next few years, Searle's petition for aspartame approval led to much disagreement within the F.D.A. The commissioner at the time, Alexander M. Schmidt, convened a three-member public board of inquiry, which concluded that one of Searle's studies on rats showed an increase in brain tumors from aspartame. The board members — all of them scientists at universities — voted to withhold approval of aspartame until more studies were done.

But yet another F.D.A. review, this one of Searle's tumor tissue slides — paid for by Searle and conducted by an academic group that is now defunct — concluded that Searle's studies had demonstrated that aspartame was safe. In 1981, a new F.D.A. commissioner, Arthur Hull Hayes, concurred with this assessment and granted approval to aspartame shortly after President [Ronald Reagan](#) appointed him to run the agency.

And in a move that fueled the conspiracy theories, Mr. Hayes left the F.D.A. a little more than a year after approving aspartame and took a job as a consultant to Burson-Marsteller, which at the time was Searle's public relations agency. Mr. Hayes did not return calls seeking comment.

Ms. Nabors of the Calorie Control Council said that suggestions or innuendoes that Searle was trying to influence government officials with lucrative job offers were baseless. Artificial sweeteners are unfairly targeted for suspicion, she said, citing the government's decision to ban the sweetener cyclamate in 1969 after studies showed

that it caused cancer in animals. "Cyclamate was banned, saccharin was required to have a warning label for a while, and there's all these conspiracy theories on aspartame," she said.

She added that there were more than 100 published scientific studies showing no adverse effects from aspartame, and said that in 2002, the European Commission reviewed many of these studies and reaffirmed the sweetener's safety. The bulk of the studies investigated neurological effects; none were animal cancer studies, which are lengthy and expensive.

In any case, critics say that most of these studies were financed either directly or indirectly by manufacturers of aspartame, and that the results of aspartame studies tend to depend on who paid for them. In an analysis of 166 articles published in medical journals from 1980 to 1985, Dr. Ralph G. Walton, a professor of psychiatry at Northeastern Ohio Universities College of Medicine found that all 74 studies that were financed by the industry attested to sweetener's safety.

Of the 92 independently funded articles, 84 identified adverse health effects. "Whenever you have studies that were not funded by the industry, some sort of problem is identified," said Dr. Walton, adding that he has not looked at studies performed since 1985. "It's far too much for it to be a coincidence."

Dr. Walton, who, like some other psychiatrists, has studied aspartame from a neurological perspective, said he had also seen problems from the sweetener firsthand. At Safe Harbor Behavioral Health, a mental health facility in Erie, Pa., where he is clinical director, Dr. Walton said he had observed that for many people with mood disorders, such as depression or bipolar disorder, aspartame exacerbates the condition. "For people with panic disorders, for instance, we've seen that when we eliminate aspartame, it's much easier to control their illness," he said. "The number of panic attacks goes down."

Dr. Walton and others say that this is probably attributable to aspartame's phenylalanine component. (Aspartame is made up of two amino acids, phenylalanine and aspartic acid.) He said that an excess of phenylalanine could upset the body's balance of neurotransmitters, causing a range of neurological symptoms.

Defenders of aspartame often point out that phenylalanine is naturally present in many protein-intensive foods. But Dr. William M. Pardridge, a professor of endocrinology at the David Geffen School of Medicine at the University of California, Los Angeles, says that when it comes from food, phenylalanine is absorbed into the brain more slowly.

"If your blood phenylalanine level was increased five times, in my view there would be a safety concern," Dr. Pardridge said. "The question is whether aspartame use could ever increase levels that much, and the answer is yes. We've known that for 20 years."

Dr. Soffritti said he had not studied the effects of phenylalanine. He theorized that the tumors in his study were related to the methanol, or wood alcohol, that is produced as the body metabolizes aspartame. When the body breaks down methanol, the result is formaldehyde, a known carcinogen. "I know that when I treat animals with methanol, you end up with lymphomas and leukemias," he said.

BUT Dr. Kenneth E. McMartin, a methanol expert and professor of pharmacology, toxicology and neuroscience at the Louisiana State University Medical Center, said he believed that it was unlikely that someone could consume enough aspartame to let harmful levels of formaldehyde build up in the body.

Dr. Soffritti said he thought that more research and open debate were needed on whether aspartame was a carcinogen. "It is very important to have scientists who are independent and not funded by industry looking at this," he said.

Michael F. Jacobson, executive director of the Center for Science in the Public Interest, a nutrition advocacy group, said he did not think that Dr. Soffritti's study could be considered definitive, but that it should prompt an "urgent re-examination.

"For a chemical that is used by hundreds of millions of people around the world, it should be absolutely safe," Mr. Jacobson said. "There shouldn't be a cloud of doubt."

*Dr. Soffritti's journal article on his findings is at [nytimes.com/business](http://nytimes.com/business).*