

U.S. Congress

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No. 106—Part II

Vol. 131

WASHINGTON, THURSDAY, AUGUST 1, 1985

No. 106

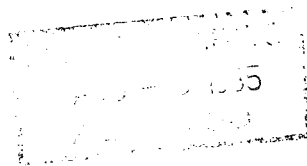
# Congressional Record

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(A) provide new budget authority or spending authority described in section 401(c)(2)(C) of such Act;

(B) relate to revenues; or

(C) specify the amount of the statutory limit on the public debt.

(7) section 405 of such Act, as added by section 4(q) of this Act, shall apply with respect to fiscal year 1988; and

(8) section 1104(c)(2) of title 31, United States Code, as added by section 5(b) of this Act, shall apply with respect to fiscal year 1988.

By Mr. METZENBAUM:

S. 1557. A bill to provide the public with information concerning the use of products containing aspartame, to provide for the conduct of studies to determine the health effects of using products containing aspartame, and for other purposes; to the Committee on Labor and Human Resources.

#### ASPARTAME SAFETY ACT

Mr. METZENBAUM. Mr. President, today I am introducing a bill entitled "the Aspartame Safety act of 1985." I consider this legislation the absolute minimum that Congress needs to do in order to protect the health and safety of the 100 million American consumers who are using this chemical sweetener under its better-known brand name of "NutraSweet."

In 1984, Americans consumed over 7 million pounds of aspartame, which is equivalent to 1.4 billion pounds of sugar. This year we will consume over 20 billion cans of diet soft drinks, the vast majority of which are 100 percent NutraSweet. We had better be sure that the questions which have been raised about the safety of this product are answered.

I must say at the outset, this product was approved by the FDA in circumstances which can only be described as troubling. The FDA originally approved aspartame in 1974. However, that decision was stayed after concerns were raised about health and safety problems. In March of 1976 a special FDA task force released its report on testing practices at G.D. Searle Co., the manufacturer of aspartame. That report contained the following conclusions:

At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the G.D. Searle Company, we have no basis for such reliance now.

Through our efforts, 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 studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies."

Now, Mr. President, one might ask what does a 1976 report on testing practices at G.D. Searle have to do with aspartame, a chemical sweetener approved by the FDA in 1981? The answer is simple. Over 90 percent of the tests submitted by G.D. Searle to

the FDA in order to get aspartame approved were submitted prior to March 1976, when the report was issued. In addition, of the 25 Searle tests examined by the FDA task force, 11 were tests done on aspartame. One of the major questions hanging over the approval process is this question of how the FDA resolved the issues raised by its own task force in 1976. There are serious questions about the quality of tests used to approve this chemical sweetener.

Mr. President, the questions do not stop with the 1976 task force report. For in 1977, the FDA wrote to the U.S. attorney in Chicago requesting a grand jury investigation of G.D. Searle Co. I quote from the letter sent by the chief counsel of the FDA, Richard Merrill:

We request that your office convene a grand jury investigation into apparent violations of the Food, Drug, and Cosmetic Act . . . and the False Reports to the Government Act, by G.D. Searle and Company and three of its responsible officers for their willful and knowing failure to make reports to the Food and Drug Administration required by the Act, and 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.

In 1980, the FDA established a public board of inquiry on aspartame. What did they conclude? "The Board has not been presented with proof of a reasonable certainty that Aspartame is safe for use as a food additive under its intended conditions of use."

In May 1981, 2 months before the FDA Commissioner, Arthur Hayes, approved aspartame for use in dry foods, three FDA scientists informed the Commissioner that they did not believe that aspartame had been proven safe beyond a reasonable doubt. They questioned the reliability of key brain tumor tests which were submitted by G.D. Searle. These three FDA scientists comprised half of the so-called "Commissioner's Team" which was set up to advise the Commissioner on aspartame approval.

Despite all the questions raised by the chronology I have outlined, the FDA Commissioner decided to approve aspartame in July of 1981. He later approved aspartame for use in soft drinks in July 1983.

In May of this year I asked the GAO to undertake a full investigation of the aspartame approval process. That investigation is now under way and I have high hopes that it will shed some light on the questions surrounding the Commissioner's decision to approve this product.

Pending the completion of that report, however, there are a number of steps which Congress should take with relation to aspartame. The bill I am introducing today outlines the minimum steps I feel are necessary.

The bill mandates that independent tests on aspartame be conducted under the auspices of the National Institutes of Health. These tests will focus on

the general effects which aspartame has on brain chemistry as well as the specific behavioral and neurological reactions experienced by individuals—headaches, mood alterations, memory loss et cetera.

The tests will also examine the health effects of aspartame on pregnant women and fetuses and whether aspartame consumption can lower the threshold for seizures. Another important area for investigation is how aspartame reacts to medicines particularly MAO inhibitors which are used in the treatment of depression, dopa used in the treatment of Parkinson's disease, and aldomet used in the treatment of hypertension.

Under the bill, there will be a moratorium imposed on new uses of aspartame in foods and drugs pending the completion of independent test or for the period of 1 year—whichever comes sooner.

These are credible questions which have been raised by eminent scientists, regarding aspartame.

Dr. Richard Wurtman of MIT has examined questions relating to aspartame's effect on brain chemistry. Dr. William Pardridge of UCLA has expressed his concerns about fetal IQ. Dr. Elsas of Emory University has warned us about groups in the population at high risk from large concentrations of phenylalanine in the blood. Dr. Matalon at the University of Illinois is particularly concerned about individuals who are genetically susceptible to phenylalanine—PKU carriers—and who may be a sizable risk group as far as aspartame is concerned. Nearly 5 million Americans are PKU carriers.

Two researchers in Philadelphia, Profs. Gautieri and Mahalik, have done studies on mice which show that aspartame affected the vision of newborn mice whose mothers had been exposed to the chemical sweetener.

Mr. President, I ask unanimous consent that reports and statements concerning these scientists be placed in the RECORD following my statement.

The PRESIDING OFFICER. Without objection, it is so ordered.

Mr. METZENBAUM. Mr. President, one final point concerning tests. The Journal of the American Medical Association recently published a report on aspartame which, with some significant disclaimers, stated it was safe for most people. I wish that this report could ease my concerns. It does not. It merely restates the FDA position which relies solely on the tests conducted by G.D. Searle. As I have indicated, these tests are under a cloud. In addition, the concerns raised recently by the scientists I mentioned above were not even considered in the report.

Mr. President, the FDA is content to have the manufacturer of aspartame, G.D. Searle, conduct these studies. How absurd. We do not need the

people who are making millions of dollars on aspartame telling us it's safe.

Has the FDA forgotten that in 1977 it sought to have a grand jury investigation into allegations that Searle conducted fraudulent tests on aspartame? Doesn't anyone in the agency know they are presently considering prosecuting that company for withholding information on adverse effects from another one of their drugs, Theo-24?

It is a sad fact that the current FDA is a mere shadow of what that agency used to be. Now it is more of a handmaiden to the food and chemical industry than it is a defender of the health and safety of American consumers.

In addition to mandating independent tests, my bill will require labeling which will inform consumers how much aspartame they are ingesting. This information is important not only for consumers who wish to regulate their intake of aspartame but also for physicians who may be treating individuals who feel they have experienced side effects. Such side effects are likely to be dose related and the physician will want to know how much aspartame has been consumed. In addition, consumers have a basic right to know the makeup of the foods which they consume.

The label will also contain the maximum allowable daily intake established by the FDA. How many consumers even know that the FDA has attached such a limit to aspartame consumption? The current ADI is 50 mg per kg. of body weight. It was originally 20 mg/kg. However, in 1983 the FDA decided to ignore its standard 100-fold safety factor by more than doubling the maximum allowable daily intake. Why did they decide to make an exception for aspartame? In 1983, they approved aspartame for soft drinks, so they decided to increase the limit knowing consumption was bound to increase. The justification the FDA used for violating its standard 100-fold safety factor was that the tests showed it was safe at the new levels of consumption. And guess who was responsible for all the tests—G.D. Searle Co., of course.

I intend to fully investigate the manner in which the FDA altered its safety standard for this product. In the meantime, consumers have a right to know at least that some such standard exists. Sure, if you weigh 130 pounds you would have to drink 4 to 5 liters of diet soft drink to hit the limit. But if you are a child who weighs 30 pounds, you hit that limit with 3 to 4 cans of diet soft drink. That's even without the gum, pudding, breakfast cereal—all sweetened with aspartame.

Under this bill, the Secretary will be responsible for deciding how best to express the ADI on the label so consumers can understand what it means. For example, on diet soft drinks the label might read: "Maximum Allowable Daily Intake: 3 cans per 25 lbs. of body weight." There may be better

ways to express this concept. The Secretary can work on that but consumers have a right to this information particularly since the advertising for this product has left the impression that everyone in the population, including children, can consume as much as they want of this chemical sweetener and still remain within the standard FDA recommended range of a 100-fold safety factor.

My bill designates one other labeling requirement. The label will advise that aspartame is not intended for infant feeding.

Mr. President, I would like to quote from an FDA document dated February 28, 1980:

Nevertheless, in consideration of the remote possibility that a parent might use aspartame as a non-sugar sweetener in the infant formula or food, there may be some merit in the inclusion of a statement on the label to the effect that aspartame-containing foods are not intended for use in infant feeding. Such labeling may provide added assurance that aspartame will not be fed to infants.

Did the FDA ever follow up on this recommendation? Of course not. Too troublesome for industry. How remote is the possibility that a parent will give nutrasweet to a child? A little diet coke in a bottle? Some pudding? A little kool-aid? Maybe some cereal?

This bill ensures that parents will know that aspartame-containing foods are not intended for infant feeding.

Finally, Mr. President, my bill will establish a Clinical Adverse Reaction Committee within the FDA. Consumers who feel they have experienced side effects from aspartame should have the right to have their complaint investigated.

The FDA claims such complaints have declined to almost zero. Isn't that interesting. What the FDA doesn't tell us is that since February of 1984, G.D. Searle has not forwarded any complaints they have received to the FDA. In addition, we learn that the FDA informed its regional office to forward only "serious complaints." IEA complaint sever enough to require the attention of a physician. And did the FDA notify physicians that they were interested in collecting and analyzing reports of adverse reactions to aspartame? Absolutely not. So how are physicians to know they should even be notifying the FDA of such reports? The only notification physicians around the country have received is a medical bulletin from G.D. Searle quoting the FDA that aspartame is completely safe.

Now, however, the FDA has informed myself and Senator HEINZ that they are considering establishing a Clinical Adverse Reaction Committee to collect and evaluate reports of side effects.

This bill makes it easy for the FDA. It mandates the FDA to collect and study reports of side effects and to alert physicians around the country that they are interested in knowing about such reactions.

Only then can we get an accurate picture of the problem.

Mr. President, I said at the outset this bill represents a minimum response to the questions which surround a response to the FDA which recently sent me a letter rejecting proposals for labeling and informing me that G.D. Searle's tests are insufficient to settle the questions raised.

To put it mildly, that response was totally unsatisfactory. We have an agency desperately attempting to explain away its unwillingness to protect the safety of American consumers. Clearly, at today's FDA politics and ideology come before the public health.

I know there are career FDA personnel who are committed to doing a good job. They are trying to be honest and professional. Their task is becoming impossible under the weight of leadership which has raised political interference to an art form. On the issue of aspartame, as on the issue of food dyes and infant formula, there are those of us in Congress who will not rest until this agency meets its responsibilities to the American consumer. That, I can promise.

Mr. President, I ask unanimous consent that the text of the bill, the letter, and scientific studies mentioned during my remarks, and other supporting materials be printed in the RECORD.

There being no objection, the material was ordered to be printed in the RECORD, as follows:

S. 1557

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Aspartame Safety Act of 1985".*

#### LABELING REQUIREMENTS

SEC. 2. (a) Section 403 of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end thereof the following new paragraph:

"(q)(1) If it contains aspartame, unless its label and labeling—

"(A) specify the total number of milligrams of aspartame contained in each serving;

"(B) specify the allowable daily intake of aspartame (in milligrams) for each kilogram of human body weight, as established by the Secretary; and

"(C) bear the following statement: 'THIS PRODUCT CONTAINS ASPARTAME, WHICH IS NOT INTENDED FOR USE IN INFANT FEEDING'".

"(2) The Secretary shall by regulation require that the information required by subparagraph (1)(B) to be specified on the label and labeling of any food containing aspartame be included on such label and labeling in a manner which is the most useful to individuals who consume such food.

"(3) The statement required by subparagraph (1)(C) shall be located in a conspicuous place on the label and labeling of each food containing aspartame as proximate as possible to the name of such food and shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling."

(b)(1) Section 502 of such Act is amended by adding at the end thereof the following new paragraph:

"(u)(1) If it is a drug containing aspartame, unless—

"(A) its label and labeling—

"(i) specify the total number of milligrams of aspartame contained in each dosage;

"(ii) specify the allowable daily intake of aspartame (in milligrams) for each kilogram of human body weight, as established by the Secretary; and

"(iii) bear the following statements: 'THIS PRODUCT CONTAINS ASPARTAME, AND IS NOT INTENDED FOR USE BY INFANTS 'PHENYLKETONURICS: CONTAINS PHENYLALANINE'; and

"(B) the manufacturer, packer, or distributor (including all retail establishments) thereof includes in all advertisements and other printed and descriptive matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to such drug the information described in clauses (A)(i) and (A)(ii) and the statements specified in clause (A)(iii)."

"(2) The Secretary shall by regulation require that the information required by subparagraph (1)(A)(ii) to be specified on the label and labeling of drugs containing aspartame be included on such label and labeling in a manner which is the most useful to individuals who consume such drugs.

"(3) The statements required by subparagraph (1)(A)(iii) shall be located in a conspicuous place on the label and labeling of each drug containing aspartame as proximate as possible to the name of such drug and shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling."

(2) The first sentence of section 503(b)(2) of such Act is amended by striking out "(and (1).)" and inserting in lieu thereof "(1), and (u)(1)(B)."

#### MORATORIUM

SEC. 3. During the period beginning on the date of enactment of this Act and ending—

(1) on the date which is one year after the date of enactment of this Act, or

(2) the date on which all studies required under section 4 are completed, whichever is earlier.

the Secretary of Health and Human Services (hereinafter referred to as the "Secretary") shall not approve or permit any use of aspartame in any food or drug if such use was not approved or permitted on the date of enactment of this Act.

#### RESEARCH

SEC. 4. (a) The Secretary, through the Director of the National Institutes of Health, shall request proposals for, and make grants and enter into contracts for the conduct of, clinical studies on aspartame, including studies concerning—

(1) the effect of the consumption of aspartame on brain chemistry;

(2) the health effects of the consumption of aspartame on pregnant women and fetuses;

(3) behavioral and neurological effects experienced by individuals who have consumed aspartame, especially children who have consumed aspartame;

(4) the interaction of aspartame with drugs, including monoamine oxidase inhibitors, alpha-methyldopa, and L-dihydroxyphenylalanine; and

(5) the effect of the consumption of aspartame in increasing the probability of seizures.

(b) In making grants and entering into contracts under subsection (a), the Secretary shall provide for the completion of the studies required under such subsection

within one year after the date of enactment of this Act.

(c) To carry out this section, there are authorized to be appropriated such sums as may be necessary.

(d) The authority of the Secretary to enter into contracts under this section shall be to such extent or in such amounts as are provided in appropriated Acts.

#### CLINICAL ADVERSE REACTION COMMITTEE ON ASPARTAME

SEC. 5. (a) The Secretary, through the Commissioner of the Food and Drug Administration, shall establish a Clinical Adverse Reaction Committee on Aspartame. The Committee shall collect reports of individual reactions to the consumption of foods containing aspartame, including reports of reactions from individuals taking various medications, and shall evaluate and prepare appropriate responses to such reports.

(b) The Secretary shall announce the establishment of the Committee under subsection (a) through the mailing of written notices to physicians and other health care providers and through advertisements in medical journals and in publications read by the general public. Such advertisements shall include the telephone number of the telephone service established pursuant to subsection (c).

(c) The Secretary shall establish a telephone service for the reporting by individuals of reactions to the consumption of products containing aspartame. Calls on such telephone service shall be without charge to the caller.

#### SCIENTISTS SUGGEST NUTRASWEET LINK TO BRAIN DAMAGE

(By Geogory Gordon)

WASHINGTON (UPI).—Two pediatric and genetic researchers say many pregnant women who consume aspartame, the popular sugar substitute sold as NutraSweet in soft drinks and 70 other products, may have babies with permanent brain damage.

In a contention rejected by NutraSweet's manufacturer, one of the scientists, Dr. Louis Elsas of Emory University in Atlanta, also said he believes a key aspartame component can cause similar damage to infants if they ingest it in the six months following birth.

"There's no reason why the pregnant female should be taking aspartame," Elsas said, "and there's no reason why a child less than six months old should be taking aspartame. Period." He said the damage may not show up for years.

Meanwhile, lawyers for a 5-year-old boy who a research team said became "unconsoled and wildly emotional" after drinking NutraSweet products have filed a \$2 million damage suit against the product's manufacturer, G.D. Searle Co. of Skokie, IL.

The suit, filed three weeks ago in Washington, charges that aspartame is an "unreasonably dangerous and harmful food additive" that causes permanent effects when combined with glucose and given to children under six years old.

It was disclosed last month the General Accounting Office is investigating the manner in which Commissioner Arthur Hull Hayes of the Food and Drug Administration approved aspartame in 1981 over the objections of several agency scientists who challenged brain tumor studies.

Officials of G.D. Searle, which last year sold more than \$600 million in NutraSweet for diet soft drinks and other products, dismiss all the allegations and criticisms of aspartame. They assert the product has undergone the most extensive testing of any food additive ever approved by the FDA.

"I think quite clearly, the data on aspartame does support the safety of the prod-

uct," Roger Thies, Searle's associate general counsel, said in a recent interview.

Dr. Lewis Stegink, a professor of pediatrics and biochemistry at the University of Iowa who, with funding from Searle, performed some of the pivotal studies that supported FDA approval, said, "Am I concerned about the safety? The answer is no. Would I like to see additional studies done? Of course. That's what science is all about."

Dr. Richard Guall, vice president for nutrition and medical affairs of Searle's NutraSweet group, said aspartame "has no adverse effects on the behavior of children" with the exception of a select group who are alerted to the contents in warning labels.

Elsas, director of medical genetics at Emory, and Dr. Reuben Matalon, professor of pediatrics and genetics at the University of Illinois Medical School, have yet to publish any findings that specifically refer to aspartame. But both said they have extensively studied a key component of the sweetener—phenylalanine—and that they consider it a hazard for fetuses and infants.

The scientists said in interviews that they approached Searle in the 1970s about their concerns, but that they believe company-sponsored studies of aspartame have not adequately tested the substance for its effects on the human fetus.

"The don't want to listen," Elsas said. "The people at Searle would like to have you think that nothing happens as long as the phenylalanine level is below the tenfold elevation level" that is the FDA's safety standard.

Elsas said that besides pregnant mothers, he is concerned about aspartame ingestion by newborn babies and young children who eat diet gelatins and puddings. He called Searle's studies on phenylalanine "a white-wash anecdote" that has received no scientific peer review. Elsas also noted that women who consume the substance while nursing could present a similar risk to their babies because the extent of phenylalanine in mother's milk has yet to be investigated.

Elsas and Matalon said consuming even moderate amounts of NutraSweet raises the concentration of phenylalanine in the blood. Matalon said he was "not too concerned" about older children consuming aspartame because the effects on them should be "reversible" through dietary changes.

Matalon, who began a study April 1 with a grant from the National Institutes of Health, said that one in 50 women are particularly sensitive to high phenylalanine consumption and if they ingest aspartame during pregnancy "it may cause birth defects" such as mild retardation. He said the defects would be a matter of concern because 8 to 10 million American women are believed to be sensitive to phenylalanine.

The affected women, Matalon said, are known as "carriers" of PKU—phenylketonuria—a disease resulting in reduced IQ's in babies. If not put on a special diet, PKU infants will suffer severe mental retardation as they grow, he said.

Although the FDA requires all aspartame products to carry a warning for PKU victims, no warnings is required for carriers, those who do not have the disease but have one PKU gene and are susceptible to phenylalanine.

The problem is complicated because carriers generally are not identified unless they have PKU offspring. "We don't know them and they don't know themselves," Matalon said.

Matalon, head of the PKU clinic at the University of Illinois, said he was concerned about studies showing that any rises in phenylalanine levels from aspartame consumption would still be within safe limits.

Matalon said those studies are "not based on a lot of experiments."

He said Searle did not adequately test the levels and effects of breakdown products—known as metabolites—of phenylalanine in the body.

Gaull and Stesink, however, defended Searle's testing and said it shows that even at "abuse levels"—extremely heavy consumption of aspartame—the phenylalanine levels in the blood do not rise significantly.

Gaull also said the levels of phenylalanine quickly drop. He said that while PKU carriers "have less ability to metabolize" than those with the disease, "it is not limiting in their ability to fully metabolize" the substance.

Consumption of aspartame, he argued, results in increases in blood phenylalanine levels "no greater than the increase in concentration after a meal . . . consisting of a hamburger and a milkshake."

Elsas, who already had published one study on humans, said he believes the potential danger extends to all present women who regularly consume aspartame, and possibly to young children who may experience behavioral and neurological disorders if they drink or eat aspartame.

Elsas said a woman who drinks one can of a soft drink sweetened with aspartame may experience a four-fold increase in her blood phenylalanine level. As a result, he said, the concentration found in the fetus can reach a level four times as high as the prospective mother's, because the chemical concentrates on the fetal side.

"Now the fetus's brain is growing, and that phenylalanine interferes at critical movements of brain cells, and that child could come out with severe mental retardation that's unrelated to anything you could measure after birth," Elsas said.

"I'm concerned that this could be a major health hazard that has been totally unexplored."

Gaull called Elsas's findings "incorrect," contending the fetus concentrates phenylalanine only at about 1.5 times the level in the mother.

Stegink called Elsas's projections of blood phenylalanine "totally impossible" but acknowledged no research has been conducted on the effect of aspartame on pregnant women.

The Washington lawsuit is based on research by Dr. Keith Connors of D.C. Children's Hospital, who said "Stephen," a 5-year-old boy "repeatedly ran full force into the wall, knocking himself to the floor, crying, and repeating the performance until we was restrained," after consuming aspartame.

The suit seeks \$2 million in negligence and liability damages from Searle due to the alleged immediate adverse effects and long-term damages to a child's neurological, or brain, nervous and motor systems.

Asked about the suit, Gaull said, "The bottom line is that aspartame has no adverse effects on children. In view of the fact that this case is in litigation, I don't want to comment on it."

Stephen's doctors allege his injuries, subject of one of numerous complaints about NutraSweet to the Centers for Disease Control, include psychotic neurosis and other neurologic and psychiatric disease and side effects, ranging from behavioral changes to nightmares.

Negligence charges, that the company failed to test aspartame, failed to warn of its possible dangers, and failed to report "adverse studies regarding the safety and efficacy of aspartame," also were lodged.

Connors, a specialist in hyperactivity and neurologic disorders in children, would not comment on his research concerning aspar-

tame. But in testimony to Congress, he said, "we are inclined to believe that the clear results . . . conclude that aspartame (and-or its vehicle) are causing deviant behavior of quite severe proportions in this boy."

"The FDA has never required adequate neurological pediatric testing to determine this kind of reaction on children. And to allow this on the market without testing it on kids is a crime," Aaron Levine, a lawyer representing Stephen, said.

Although Searle officials maintain the product is safe, four company-sponsored tests—investigating aspartame's possible effect on hyperactivity and seizures in children, seizures in adults, and headaches—are under way.

#### STUDY ON MICE SHOWS ASPARTAME PROBLEMS, RESEARCHERS SAY

PHILADELPHIA (AP).—Two researchers are calling for further studies into the effects on pregnant women of the artificial sweetener aspartame, saying that their study using mice showed that offspring had trouble with their eyes.

Aspartame is sold as a sugar substitute under the trade name Equal and as an additive under the name Nutrasweet.

"We don't advocate stopping the use of aspartame, but we do think there is a need for more studies on its use by pregnant women," said Ronald F. Gautieri, professor of pharmacology at the Temple University School of Pharmacy.

Gautieri and Michael P. Mahalik, assistant professor of pharmacology at the Philadelphia College of Osteopathic Medicine, reported their findings in a recent issue of Research Communications in Psychology, Psychiatry and Behavior.

In their study, the eyes of newborn mice whose mothers were not exposed to aspartame began focusing 20 days after birth. Babies born to pregnant mice fed 1 gram of the sweetener per kilogram of their weight took 2 days longer to focus, and 4 grams extended the focusing time to 4 days.

"Something affected the neurosensory system," Gautieri said.

In the last year, a growing number of researchers have warned pregnant women to avoid aspartame because of unknown consequences to fetuses.

"Something could happen over the long term," Mahalik said. "We feel that byproducts of aspartame somehow affect the process of myelination, the sheath that covers nerves."

"We think the study supports the previously-stated opinion that aspartame could affect some brain functions."

The Food and Drug Administration and the National Centers for Disease Control, reacting to more than 500 consumer complaints of headaches, dizziness, and insomnia, have said tests reveal no problems with the sweetener. But the CDC also said it did not examine any possible problems relating to pregnancy.

The National Institutes of Health is conducting a 3-year study on aspartame.

The FDA's acceptable daily intake of the sweetener is 3 grams for a person weighing 130 pounds. That is equivalent to six quarts of soda containing Nutrasweet or 150 packets of Equal.

#### GAO INVESTIGATING NUTRASWEET APPROVAL (By Gregory Gordon)

WASHINGTON (UPI).—The General Accounting Office is investigating the manner in which the Food and Drug Administration approved the popular artificial low-calorie sweetener aspartame in 1981 over the objections of several agency scientists, it was disclosed Wednesday.

The inquiry was begun at the request of Sen. Howard Metzenbaum, D-Ohio, who said in a letter last week to Comptroller General Charles Bowsher that there were "serious deficiencies" in tests more than a decade ago on the product—marketed as NutraSweet by the G.D. Searle & Co.

Officials of G.D. Searle, a Skokie, Ill.-based firm that last year sold more than \$600 million in aspartame, said Wednesday they are absolutely convinced the product, widely used in diet soft drinks, is safe.

They acknowledged they have commissioned eight new studies on the effects of the sweetener on humans, including whether it may be linked to intense headaches, seizures in children and adults and hyperactivity in children—all subjects of hundreds of consumer complaints filed with the Centers for Disease Control.

Dr. Gerald Gaull, vice president for nutrition and medical affairs of Searle's NutraSweet group, said the FDA had concluded the company's earlier studies were sound. He said Searle is conducting new tests, four of which should be completed by early next year.

"If there is a real problem we'd better be the first ones to know because we're going to need some lead time to correct it, take the product off the market, or whatever," Gaull said.

James Turner, a Washington consumer lawyer who has challenged the FDA's approval process that began in the early 1970s, asserted that "Searle's undertaking of these new tests is an admission that this product has not been shown to be safe for marketing."

Turner is appealing a federal court lawsuit aimed at forcing the FDA to hold public hearings on the safety of aspartame.

Internal government memoranda obtained by the United Press International show that Commissioner Arthur Hull Hayes of the Food and Drug Administration overruled several agency scientists in approving G.D. Searle's application to market aspartame in 1981.

Three of six scientists on the "Commissioner's Team on Aspartame" said on May 18 and 19, 1981, that tests they had reviewed did not prove the product's safety with "reasonable certainty of no harm," as required by FDA regulations, according to agency memo obtained by UPI intern Joshua Meyer.

Metzenbaum last week asked the FDA to require labels showing the amount of aspartame a product uses; to ensure that "focused clinical tests" take place; and to commission a qualified independent lab to repeat the animal tests questioned by the FDA researchers.

In his letter to Bowsher, he said that "very serious questions have been raised regarding this approval process, questions which must be resolved if consumers are to have complete confidence in the safety of aspartame."

GAO officials confirmed that Congress' investigative arm is following up on Metzenbaum's request for an inquiry into:

The validity of G.D. Searle's tests on brain tumors in rats, challenged in 1975 for being sloppy and unscientific by an FDA task force and criticized again by the three scientists on the panel advising Hayes.

Why Hayes overruled the FDA-appointed Public Board of Inquiry, which opposed the approval of aspartame in 1980 on grounds the brain tumor studies were inadequate. Walle Nauta, chairman of the board of inquiry, has indicated the panel may have opposed the approval even more strongly had it known that G.D. Searle planned to widely market it in soft drinks. Nauta has said that

a different set of tests should have been conducted for soft drink use.

Roger Thies, Searle's associate general counsel, asserted in an interview Wednesday that the likelihood aspartame would be used in carbonated beverages was made clear to the board and that the dosages tested proved safety of aspartame as a food or beverage additive. He said, "It would be almost inconceivable to me that somebody could drink enough (diet) soft drink in a day to go beyond the consumption levels that we have shown to be safe."

Hayes' decision to overturn the board of inquiry based on a summary of a "Japanese study" submitted after the board's decision. The study, UPI learned, was conducted by the Ajinomoto Co., Inc., the Japanese licensee of Searle's aspartame patent. Turner has alleged that Hayes had no legal basis to rely on a study that was not part of the administrative record.

The extent the FDA evaluated the concerns of Dr. Richard Wurtman of the Massachusetts Institute of Technology, who raised questions with the FDA regarding the effects of aspartame on brain chemistry, and Dr. William Partridge of UCLA, who suggested women who consume aspartame may give birth to infants with lower I.Q. levels.

Whether officials of the Carter White House, Reagan White House or Reagan transition team discussed aspartame approval with FDA officials. Thies denied that Searle Chairman Donald Rumsfeld, a former top aide to President Gerald Ford, had any contact with White House or FDA officials about aspartame after joining the firm in 1977.

The same tests questioned by FDA scientists continue to be the foundation of proof of safety relied on by the agency in approving NutraSweet.

Gaull contended that aspartame, the three components of which are aspartic acid, phenylalanine and methanol, is "the most tested product ever approved by the FDA."

The Centers for Disease Control in Atlanta recently issued a report on the side effects of aspartame on humans, asking the FDA to start "focused, clinical studies" on the product's safety on "an expedited basis."

Two-thirds of 200 complaints reviewed in the report were considered adverse neurological or behavioral reactions—*anxiety, seizures, extreme headaches, dizziness, severe depression and mood swings.*

Other reactions consumers have blamed on the sweetener include the formation of benign skin tumors, menstrual irregularities and many other problems.

Thies said a small segment of the 100 million Americans who have tried aspartame products may have a "sensitive or allergic reaction, or idiosyncratic reaction" to aspartame.

In opposing aspartame approval, three of the six FDA scientists advising Hayes focused on G.D. Searle's brain tumor studies and concluded that aspartame "has not been shown to be safe and therefore may not be approved for marketing," the term head wrote in 1981.

One of the three, Dr. Satya Dubey, said in a letter to team leader Joseph Levitt that "statistical results obtained so far point out many problems . . . and some of them may be considered serious."

Also objecting were Dr. Robert Condon and Dr. Douglas Park, the staff science adviser for the FDA Office of Health Affairs.

Gaull said that although "three internal scientists raised questions about the brain tumor studies and the statistics on that, there is nothing new about the fact that not

everyone agrees within a regulatory agency on every decision."

[From the New York Times, July 3, 1985]

#### A SWEETENER'S EFFECTS: NEW QUESTIONS RAISED

(By Marian Burros)

In 1984, G.D. Searle & Company of Skokie, Ill. sold \$600 million worth of the artificial sweetener aspartame, on which it holds the exclusive United States patent. Produced under the trademark NutraSweet as a food additive and Equal as a table-top sweetener, aspartame is found in a wide variety of products—from puddings, bubble gum and breakfast cereals to some of the best known diet soft drinks marketed by Coca-Cola, Pepsi and Seven-Up.

Recently, however, aspartame has been the target of criticism from several scientists conducting studies of the sweetener or its components. While their findings are not conclusive, preliminary data have indicated that aspartame may be responsible for a range of problems from temporary dizziness to mental retardation.

Their contentions are strongly denied by Searle, which has done its own studies on aspartame in the past and is conducting new ones. "When any new product is marketed and attention is called to it, people tend to ascribe any adverse experience to that new product," said Dr. Frank M. Sturtevant, a pharmacologist who is director of the office of scientific affairs at Searle. "We expected a lot more in the way of complaints than we got: only 600 out of 70 million people who have used it."

Aspartame has been controversial since Searle first sought to market it in 1974. After considerable debate about its safety, the sweetener was approved by the United States Food and Drug Administration in 1981. But this spring questions about its effects began to surface again.

In May, the Senate Committee on Labor and Human Resources received testimony from two researchers favoring quantitative labeling of products containing aspartame. In accordance with Federal law, it is now listed on labels as an ingredient; no amount is specified. Dr. William Partridge, an associate professor of medicine at the University of California at Los Angeles, said that too much of the artificial sweetener might cause subtle brain changes in young children. Dr. Richard J. Wurtman, director of the clinical research center at the Massachusetts Institute of Technology, said that consuming aspartame with carbohydrates might double aspartame's effect on the brain.

On June 17, Dr. Louis Elsas, director of the division of medical genetics at Emory University in Atlanta, said that neither pregnant women nor infants under the age of 6 months should consume aspartame because of the chance of brain damage to the fetus or infant.

Dr. Sturtevant, who calls these contentions "at best, highly speculative," says dozens of tests done by Searle prove the safety of aspartame. Dr. Sanford Miller, director of the F.D.A.'s Center for Food Safety and Applied Nutrition, says that the claims against aspartame are unfounded. And the American Diabetics Association has reaffirmed its faith in aspartame, saying that F.D.A.'s studies "appear sufficient to demonstrate its safety."

Since the marketing of aspartame four years ago, the Centers for Disease Control in Atlanta has received over 600 complaints from people who said they suffered dizziness, headaches, blurred vision or grand mal seizures (a type of epilepsy) after consuming aspartame. The centers called for studies to

determine individual sensitivity to the sweetener.

On May 23, a \$2 million lawsuit was filed against Searle in United States District Court in Washington on behalf of a 5-year-old boy in Olney, Md. The suit charged that consumption of NutraSweet caused irreversible brain damage, but it did not specify the amount consumed.

In granting approval of aspartame—which is 180 to 200 times sweeter than sugar with only one-tenth of the calories—Dr. Arthur Hull Hayes Jr., the F.D.A. Commissioner in 1981, overruled several of the agency's scientists and an independent public board of inquiry set up to evaluate the Searle studies of aspartame's effect on animals. These scientists said that the company's research did not adequately answer the safety questions about carcinogenicity. According to Congressional testimony from Dr. Alexander M. Schmidt, a former F.D.A. Commissioner, some of the experiments were "poorly conceived, carelessly executed or inaccurately analyzed or reported."

After a recent review of the Searle studies, Dr. M. Adrian Gross, a senior science adviser at the Environmental Protection Agency and a former pathologist at the F.D.A., wrote to the office of Senator Howard M. Metzenbaum, a member of the Committee on Labor and Human Resources. His letter said that despite the shortcomings of the experiments, "at least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals."

In a telephone interview, Dr. Sturtevant asserted that some of the data presented to Dr. Gross for review were incorrect. The correct tabulations, he contended, were contained in a document that he wrote for the board of inquiry impaneled by the F.D.A. The document showed, he said, "that there is no statistically significant increase in brain tumors in experimental animals."

Aspartame-sweetened foods now carry a warning directed at phenylketonurics—people who are unable to metabolize phenylalanine, one of two amino acids that make up aspartame. Victims of phenylketonuria, or PKU, will become permanently retarded if the condition is not diagnosed at birth and consumption of phenylalanine strictly controlled.

According to Dr. Elsas, about 2 percent of the population are carriers of the PKU gene and are unaware of the condition. He has expressed concern about the effects of phenylalanine on unborn children of PKU carriers.

"A small change in the phenylalanine level in a pregnant woman's blood is magnified by the placenta into the fetal blood, and the fetal brain will concentrate that further," Dr. Elsas explained. "High levels of phenylalanine in unformed or forming brains could cause irreversible damage. No one knows what degree of elevation in the mother's blood may cause brain damage in the fetus."

Dr. Elsas's concern is based on two studies of the effects of phenylalanine on two groups of people—10 in each group ranging in age from 8 to 24—who have PKU but have developed normally. In these studies, the first of which was published in the *Journal of Clinical Investigation* in January, Dr. Elsas observed that the patient's reaction time was affected and the production of adrenalinlike chemicals in the brain was reduced.

The second study, just completed, confirms the first, he said, adding, "All of the brain changes were reversible within a three-week period, but it took longer for full mental functions to return."

Dr. Elsas said that anybody over the age of 6 months should consume "aspartame in moderation, and if they have symptoms, they should get their phenylalanine blood level checked."

Dr. Sturtevant says that Dr. Elsas "is scaring people unnecessarily." "It is not physically possible for an unknown PKU carrier to maintain a phenylalanine blood level in the unsafe range by means of consuming products containing NutraSweet," he said. "There is no experimental evidence to suggest a risk to the fetus." Searle has eight studies of its own under way exploring the effects of aspartame on the brain.

Dr. Wurtzman of M.I.T. does not believe that moderate amounts of aspartame are a hazard to normal people. "But" he said in a recent interview, "I think there are some numbers of people who are at risk." Dr. Wurtzman, who is a consultant to Searle on products other than aspartame, said that when he and Searle "talk about aspartame we tend not to agree."

Dr. Wurtzman's own animal studies show that "you double the effect of the phenylalanine in the brain when you have aspartame and carbohydrates together, and no one knows what a safe amount is," he said. "There are several groups of people who might be especially susceptible to high doses. These include people who are taking drugs that act on the brain like antihypertensives, people with a history of seizures, young people and pregnant women." For adults who do not fall into the above categories, Dr. Wurtzman said half a gram to one gram of aspartame a day should be safe.

"But," he added, "if a 7-year-old, weighing about 45 or 50 pounds, drinks a 2-liter bottle of Diet Coke, which contains about 1,200 milligrams, he is already exceeding the allowable daily limit for aspartame suggested by F.D.A."

Dr. Wurtzman said he knew of a dozen patients "with first-time seizures confirmed in university hospitals who were consuming very large amounts of aspartame." "It is very important," he said, "that such people be subjects in controlled studies."

Dr. Wurtzman also said all foods containing aspartame should state the amount on the label.

But Searle and soft-drink manufacturers disagreed. "We have no objection to F.D.A. requiring quantitative labeling for food ingredients in general," Dr. Sturtevant said, "but we do object to F.D.A. singling out aspartame, because there is no scientific evidence suggesting that it need be."

"Aspartame is safe," said Dr. Miller of the F.D.A., but he added: "We are not moving very rapidly to approve new uses. If there is another segment of the population besides phenylketonurics who are sensitive, we will do whatever we have to do—from putting something on the label up to banning it if the population is large enough."

[From The Washington Post, July 3, 1985]

#### EXPERT STILL TROUBLED BY ASPARTAME

(By David Zinman)

Aspartame, the low-calorie sugar substitute marketed as NutraSweet, is one of the amazing success stories of the 1980s. In the four years since the artificial sweetener found its way onto grocery store shelves, more than 100 million Americans have tried it. They have tasted it in more than 90 types of products ranging from diet soft drinks to sugarfree gum. Last year, its manufacturer, G.D. Searle & Co., reported sales soaring to \$535 million. By 1986, some expect it to top \$1 billion.

But there is a possible dark side to all this. Aspartame contains a potentially harmful component, an amino acid called phenylalanine.

Too much of it can cause brain damage, especially in fetuses and newborn of genetically susceptible women, according to studies done by Dr. Louis Elsas of Emory University in Atlanta.

"The big unanswered question," said Elsas, "is if pregnant women taking artificial sweeteners can elevate their blood level of phenylalanine to concentrations that adversely affect their fetuses. Is the damage from phenylalanine produced by a threshold effect? Or do little bits of the problem occur at lower levels?"

"Aspartame is being promoted as something good for you. But I don't think that it is a legitimate thing for our nation to be exposed to in large quantity."

Searle said reports about potential adverse effects of aspartame on pregnant women and infants were "misleading and do a disservice to consumers." The Chicago-based firm pointed out that in 1981, the Food and Drug Administration found the product to be safe and effective.

Searle does not dispute the contention that high levels of phenylalanine can cause damage in fetuses. But it says there is no cause for alarm because current consumption amounts are not even close to a point where they might pose a problem. Most important, it says that studies on pregnant animals show that even at "abuse levels," aspartame presents no hazard to the fetus.

Nonetheless, Elsas, director of medical genetics at the Atlanta school, said he is concerned, in part, because the sweetener's sale has been so massive and there are still some unknowns about the product. What worries him—and this is not based on any study but his own personal thoughts as a scientist—is the notion that aspartame's effects could be slow and subtle. They could take a generation or more to uncover.

"It's not going to be so overt an explosion," Elsas said recently on "Nightline," an ABC-TV news program. "We may not be able to see the effects for a generation. And then we'll suddenly see a lot of kids with behavioral abnormalities—with IQs that aren't reaching what . . . we anticipated from their educational or their genetic input."

Searle says that more than 20 years of testing in animals has shown aspartame to be safe over long periods. Elsas acknowledges there has been no documented negative side effects of aspartame. Nor has he personally conducted a study on the sweetener.

But he has done research with children and young adults with gene defects who ingested phenylalanine at high levels and found that their reaction time had slowed. That means phenylalanine can produce quantifiable changes in brain function. "I believe," he says, "the unlimited use of phenylalanine products should be moderated especially in certain groups."

A pediatrician and a biochemist, Elsas is focusing on patients with a rare genetic disorder called phenylketonuria or PKU. These individuals cannot metabolize foods containing phenylalanine. As a result, the chemical concentrates in their brains. This can cause retardation in fetuses and newborns who have this genetic disorder. Many states require tests to discover PKU babies who must then be kept on special diets.

Elsas is also concerned about parents of these children, who are normal but may carry one of the two genes needed to have PKU. "There is a genetically susceptible subpopulation of well over a million women whose fetuses may be at risk if they take indiscriminate amounts of phenylalanine," says Elsas. They, too, he says, may also have an impaired ability to metabolize phenylalanine.

Since it is not always possible to detect these single gene carriers before a PKU baby is born, the vast majority don't know who they are. About 1 percent of babies delivered each year are born to mothers who are PKU carriers.

People in whom high levels of phenylalanine may pose problems, Elsas said, are:

Pregnant women. If blood phenylalanine rises to a level high enough to cause problems, the child's brain development could be affected.

Children under 6 months. A high level of blood phenylalanine can produce irreversible brain damage by slowing formation of mature brain cells and by altering the formation of myelin cells that insulate parts of the brain.

Older children and adults carrying the PKU disorder. A high blood concentration of phenylalanine will reduce the brain's ability to function as quickly and efficiently. But these changes are reversible once the level of phenylalanine returns to normal.

The flaw in Elsas' argument, says Daniel Azarnoff, president of research and development for Searle, is that he has no idea what is a dangerous level of phenylalanine concentration. Moreover, he said, Elsas' concern that people may be getting toxic amounts of phenylalanine flies in the face of scientific data. "He is saying people eat a lot of aspartame," says Azarnoff. "The evidence is they don't."

The FDA has set 50 milligrams of aspartame per kilogram (2.2 pounds) of body weight as an acceptable daily intake. To reach that amount, Searle says, a 132-pound person would have to drink 18 cans of diet soda in a day. The average 12 oz. can of diet soda contains 170 milligrams aspartame, Searle says.

But Dr. William Patridge of the University of California at Los Angeles says the FDA has underestimated consumption of aspartame. Patridge could not be reached for comment. However, the magazine Common Cause said Patridge wrote to the FDA in 1983 citing figures showing how children eating aspartame-sweetened foods all day could be on their way to consuming the maximum amounts the FDA uses for its safety assessment.

Searle says that tests it sponsored show no harmful effects have been seen even at levels of 200 milligrams—four times the FDA's intake standard. However, the quality of Searle-sponsored studies has been criticized. Sen. Howard Metzenbaum (D-Ohio) has complained that the FDA overruled many scientific questions raised about the reliability of testing. A federal investigation is now under way.

Elsas also argues that the FDA's own publications show that the daily phenylalanine intake of some children ages 7 to 9 goes as high as 70 milligrams per kilogram of body weight—exceeding the agency's acceptable daily amount of 50 milligrams. What Searle's studies do not show, he says, is long-term effects at intermediate levels. In addition, one scientist, Richard Wurtzman of the Massachusetts Institute of Technology, says some foods intensify the effects of phenylalanine. "If one drinks a beverage containing aspartame at the same time one eats a carbohydrate-rich food," Wurtzman says, "then aspartame's effect on brain phenylalanine is doubled."

To try to clarify the situation, Dr. Reuven Matalon of the University of Illinois has started a study funded by the National Institutes of Health to look at the effects of aspartame on PKU carriers as well as on normal individuals. The study will take about two years.

"In the meantime, I don't think it is fair to express concerns about aspartame as conclusions," he said. "There is no data to implicate it in any difficulty. At the same time, we do not know what a high level of intake will do and where the danger point comes. Until we get the data, if I were the FDA, I would recommend that pregnant women use caution. Moderation should be the key."

#### SWEET SUSPICIONS

**STEVE WILSON.** They say it's the biggest breakthrough in diet drinks, a better taste from a new product everybody is talking about.

#### Commercial.

**STEVE WILSON.** 7-up has got it, too. And orange soda, and Dr. Pepper. And the fact is it's virtually impossible to find a can of diet soda without NutraSweet.

#### Commercial.

**STEVE WILSON.** Powered drink mixes have it too, like Kool-Aid, Wylers fruit drinks, chocolate drink mixes. It's in Jello, it's in all kinds of sugar-free products. You can buy it in little packets under the brand name Equal. It's 200 times sweeter than sugar and Americans sure like the way it tastes. The company that makes it at \$80 a pound made more than half-a-billion dollars worth last year and may sell twice as much in 1985—unless nagging safety questions slow down sales.

**MOS.** My girlfriend just told me yesterday it's not supposed to be good for you. So, now I'm not too sure if I'm drinking the right thing.

**MOS.** I'd like to know how safe it is. I imagine it is safe to a degree because it's in everything you drink now-a-days.

**ROBERT SHAPIRO.** It's safe.

**STEVE WILSON.** Unquestionably?

**ROBERT SHAPIRO.** Unquestionably!

**STEVE WILSON.** Not a doubt in your mind?

**ROBERT SHAPIRO.** Not a doubt in my mind.

**STEVE WILSON.** Nobody expresses more confidence in the stuff than the man who is president of the NutraSweet Group, the division that brings in 70 percent of the total profits of the big Searle Pharmaceutical Company.

**STEVE WILSON.** Why is it that you can't seem to convince so many others of that?

**ROBERT SHAPIRO.** That's just not right. The fact is we have convinced all the folks whose opinion matters.

**STEVE WILSON.** He's not talking about Joyce Moscato. She's one of thousands of people who have complained about serious side effects, one of those who believes when all the facts are known.

**JOYCE MOSCATO.** Everybody's going to be convinced that there are people who do have an adverse reaction to the consumption of NutraSweet.

**STEVE WILSON.** Mary Carr is another one who's not convinced by Searle's multi-million-dollar advertising and public relations blitz.

**MARY CARR.** My body went through hell with this stuff, I really did. I think that they should take it off the market and do more research because I would not want to put anyone through this.

**STEVE WILSON.** But it's not just all the letters from consumers who are reporting adverse effects. It's what so many respected scientists are saying.

**DR. WOODROW MONTE.** Every time a truly impartial team of scientists have looked at NutraSweet, it has been turned down, it has been denied. It's not been tested correctly. The tests that have been done that I consider to be honest tests show extreme dangers over the long term.

**WILSON.** When our report continues, a closer look at some of the complaints and

why some scientists are still saying that despite government approval, your diet soft drink may not be as safe as you've been led to believe.

**STEVE WILSON.** Are you telling me I shouldn't drink the stuff?

**DR. WOODROW MONTE.** Yes, I am saying you shouldn't drink the stuff.

**STEVE WILSON.** It's dangerous.

**DR. WOODROW MONTE.** Yes, I'm saying that I believe that with all my heart.

**ROD LEONARD.** Seizures, headaches; among women it's the early onset of menopause, serious depression. People say they can't understand what's happening to them except that they keep getting more and more depressed until they want to kill themselves.

**JOYCE MOSCATO.** You really don't want to go to work, you don't want to deal with friends, you don't want to communicate with the rest of the world.

**STEVE WILSON.** They believe Nutrasweet, America's newest artificial sweetener, is responsible. And despite how good it tastes in diet drinks and gelatin and all kinds of sugar-free products, people all over the nation are reporting side effects. Like headaches—some mild, some unbearably painful; stomach problems; various allergic reactions, even seizures. But her complaints and thousands of others like them are "anecdotal", scientifically unsubstantiated stories that don't worry Robert Shapiro.

**ROBERT SHAPIRO.** No, I don't find it scary because I'm aware of what the evidence is and there is no evidence to suggest that younger females or anybody else has a problem with the product.

**STEVE WILSON.** He's president of the group that makes it, the Nutrasweet Group at the G.D. Searle Drug Company where they can't ship it fast enough to meet demand. But on Capitol Hill just last month, FDA chairman Frank Young admitted to a Senate Committee that while he believes it's safe for most of us, there is a big exception.

**FRANK YOUNG.** With the exception of a sub-group in the population, young females and that is under further study at this point.

**STEVE WILSON.** But diet drinks are big with lots of young women, a number of whom have reported the same problem Joyce Moscato had for the many months she consumed NutraSweet—her menstrual periods simply stopped.

**JOYCE MOSCATO.** December 27th I quit using NutraSweet and on January 25th I had my first period. I felt great and I've been normal ever since.

**STEVE WILSON.** Well, despite his claims nobody has a problem with his product, Shapiro knows better and reluctantly admitted NutraSweet—aspartame—can be trouble.

**ROBERT WILSON.** Now it's not just young women reporting side effects. Some of the nation's most respected scientists have some serious concerns about the product. Dr. Richard Wurtman at MIT believes it may adversely affect brain chemistry; that is can cause behavioral changes. Dr. John Olney at Washington University has raised questions about brain damage to children. And here on the campus of Arizona State University near Phoenix, Dr. Woodrow Monte says the big danger is from a substance left in our bodies when NutraSweet breaks down—methyl alcohol.

**DR. WOODROW MONTE.** If I could get a public hearing, if I could have a Congressional hearing, if I could have a hearing before the Food and Drug Administration which they have been stopping, trying to stop, I could prove easily, show easily, that even these so-called small amounts of methyl alcohol can cause extremely serious consequences over the long term.

**STEVE WILSON.** Now these complaints we've been hearing from all over the country are certainly alarming but what may be even more alarming is how this product NutraSweet got past the Food and Drug Administration and onto our grocery shelves.

**STEVE WILSON.** Politics?

**ROB LEONARD.** I would call it politics.

**STEVE WILSON.** Steve Wilson (reporting).

**JOYCE MOSCATO.** Never for one minute did I suspect that a product that was on the market with the approval of the FDA would be causing such harm.

**STEVE WILSON.** Joyce Moscato and many others like her say the harm—in her case depression and menstrual problems—is linked to NutraSweet. The only artificial sweetener the Food and Drug Administration has declared safe.

**ROBERT MCQUATE.** For FDA to cavalierly approve something on a whim is totally out of the realm of possibility.

**STEVE WILSON.** But you weren't satisfied with the work that they'd done?

In fact the soft drink makers were so dissatisfied with what they believed was the lack of evidence NutraSweet was safe, they prepared a formal, 31-page protest—scientific chapter and verse raising serious questions. McQuate says now it was just designed to "spark discussion in the industry"—and it never WAS submitted to the FDA. He says secret tests his members paid for later answered all their questions. But others believe those who want to use NutraSweet discarded the scientific concerns for safety in favor of higher profits brought in from better-tasting diet products. But Searle—the big drug company—makes NutraSweet and has the legal responsibility to scientifically prove to the government that it's safe.

**DR. ADRIAN GROSS.** They lied and they didn't submit the real nature of their observations because had they done that it is more than likely that a great number of these studies would have been rejected simply for adequacy.

**STEVE WILSON.** Dr. Gross was the chief scientist on a nine member task force that reported Searle made a number of "deliberate decisions" seemingly calculated to minimize the chances of discovering NutraSweet is toxic—a danger to our health.

**DR. GROSS.** What Searle did, they took great pains to camouflage these shortcomings of the study. As I say filter and just present to the FDA what they wished the FDA to know and they did other terrible things for instance animals would develop tumors while they were under study. Well they would remove these tumors from the animals.

**STEVE WILSON.** Other laboratory animals Searle used for tests on another product in the same lab seemed to die and come back to life—this one three times.

**ROBERT SHAPIRO.** It's apparently a recording keeping error.

The president of the NutraSweet Group at Searle says Dr. Gross and his task force are just wrong. But looking at other experiments on laboratory animals and other independent evidence, a scientific board of inquiry has also raised serious safety questions. So have other respected scientists. But the FDA approved it. So it's safe?

**ROBERT SHAPIRO.** It has been established by the people who are charged by law with the responsibility for making those decisions and they've made those decisions and the fact is it's safe.

Everybody who has looked at the cancer question has said this should not be marketed on the basis of the cancer question except for Dr. Hayes. The Reagan appointed commissioner of the FDA who now works

as senior medical advisor to the Searle public relations firm.

STEVE WILSON. Dr. Arthur Hayes who approves wider use of NutraSweet is also now dean of the New York Medical College and refuses to speak publicly about this issue.

WILSON STAND-UP. Now we don't know if NutraSweet is safe or not. We do know that a lot of good scientists still have a lot of good questions and that's the point: The law requires the FDA to establish to a reasonable certainty that the stuff is safe before we start consuming it. About all that's certain at this point: there's big money riding on the outcome and so too is our health. At Searle Company headquarters in Chicago. (Steve Wilson reporting).

#### NUTRASWEET UP-DATE

COMMERCIAL. "It's a little red swirl next to the name NutraSweet Brand Sweetener."

STEVE WILSON. Thanks to a fortune spent on ads like this, even young Americans know what NutraSweet is.

COMMERCIAL. "100 percent NutraSweet. Oh, that's the good stuff."

WILSON. But since we reported more about all the questions still unanswered in regard to the safety of NutraSweet, there have been some new developments.

Sen. HOWARD METZENBAUM. There's enough reason to be suspicious.

WILSON. Senator Metzenbaum says he's seen enough now to have real suspicions and he has directed the General Accounting Office to investigate. Specifically, his letter to the Comptroller General asks for an investigation of NutraSweet test results, what really happened during the formal FDA approval process, and to what extent was the White House involved in the approval of the product.

Sen. METZENBAUM. Where there's smoke, there's fire. The Food and Drug Administration ought to act with dispatch to investigate these, the safety of this product. Too many people are drinking too many diet drinks to permit this to go on and they shouldn't need a Congressional prod in order to do the job that is truly their own responsibility.

WILSON. By the way, another Metzenbaum letter, this one also signed by Senator Heinz, puts some sharp questions to the F.D.A. The Senators want to know if more stringent labeling requirements are in the works. So we'll know how much of the stuff is safe to drink, what's being done to validate the test data the manufacturer provided, and who's monitoring and encouraging medical reports from doctors across the nation when they see evidence of medical problems possibly related to NutraSweet?

Searle—the maker of NutraSweet—is still standing behind the product, calling it absolutely safe. But the company has acknowledged now at least eight more studies are being done on the product safety questions, perhaps the biggest here at Duke University. Scientists on this campus and elsewhere will study whether NutraSweet causes headaches, seizures and special problems for children.

In Atlanta, scientists at Emory University are out with a report that links NutraSweet consumption by pregnant women to birth defects and problems with infants who eat or drink it. And in Maryland late last month, what may be the first lawsuit as a result of the safety concerns. The mother of a little boy is seeking \$2 million from Searle claiming the child has suffered serious and permanent neurologic and psychiatric injury as a result of NutraSweet.

The product, meanwhile, is still selling briskly. Sales are expected to top \$1 billion this year.

#### DEPARTMENT OF HEALTH,

#### EDUCATION, AND WELFARE,

Rockville, MD, January 10, 1977.

Hon. SAMUEL K. SKINNER,

U.S. Attorney, Northern District of Illinois,  
219 South Dearborn Street, Chicago, IL.

DEAR MR. SKINNER: We request that your office convene a Grand Jury investigation into apparent violations of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(e), and the False Reports to the Government Act, 18 U.S.C. 1001, by G.D. Searle and Company and three of its responsible officers for their willful and knowing failure to make reports to the Food and Drug Administration required by the Act, 21 U.S.C. 355(d), and 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. Concealing material facts relative to the Aldactone study also resulted in that drug being misbranded within the meaning of 21 U.S.C. 352(a) and 321(n), in violation of 21 U.S.C. 331(a).

#### I—THE STATUTORY/REGULATION SCHEME

A. *Investigational New Drugs.* The Food and Drug Administration has responsibility for assuring that drugs marketed in this country are safe for their intended uses and are accurately labeled. The Federal Food, Drug, and Cosmetic Act prohibits the marketing of any "new drug" in interstate commerce unless a new drug application (NDA) filed pursuant to 21 U.S.C. 355 containing substantial evidence of the safety and effectiveness of the drug has been approved by the FDA. Before an NDA is approved for any particular use of a drug, that drug may lawfully be used only for investigational tests, first in animals and thereafter in humans. This testing is permitted only in accordance with 21 U.S.C. 355(d) and regulations promulgated thereunder.

The original statutory basis for regulating the investigational use of new drugs was provided in 1938 by the basic Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962 authorized the FDA to establish by regulation new reporting requirements to assure that information about significant hazards, contraindications, side effects and adverse or unusual reactions associated with the investigational use of new drugs is disseminated rapidly. These regulations specify the form, content, and timeliness for the submission of such reports. Failure to comply with such requirements is prohibited under the Act, 21 U.S.C. 331(e).

A major purpose of the investigational drug regulations, 21 CFR Part 312, is to safeguard human subjects during the investigational phase of drug development. Accordingly, the regulations require that prior to the administration of any investigational drug to human subjects, the sponsor of the drug must file with the FDA a notice of claimed investigational exemption for a new drug (IND), which contains adequate information about preclinical (animal) investigations of the drug and any studies and other experience from which the sponsor has concluded that it is reasonably safe to initiate clinical (human) testing. A careful evaluation of the animal toxicity and pharmacological studies provides some assurance of the expected effects when the drug is administered to humans. If the data submitted in an IND justify the conclusion that the drug may safely be tested in humans, the FDA permits the sponsor to ship the drug to investigators. It is not uncommon, as is the case with Aldactone, that a drug may have an approved NDA for certain uses while simultaneously being tested in animals and/or humans for other uses under an IND.

Because the IND procedures provide a limited exemption for the distribution of a drug which has not as yet been shown to be safe and/or effective by adequate and well-controlled clinical investigations, the regulations require the sponsor to closely monitor the progress of pre-marketing investigations. The regulations provide that progress reports of such investigations be submitted to the FDA at reasonable intervals, not to exceed one year. 21 CFR 312.1(a)(5). In addition, the regulations require that a sponsor shall "promptly investigate" and report to the FDA "any findings associated with use of a drug that may suggest significant hazards, contraindications, side effects or precautions pertinent to the safety of the drug". If such a finding is "alarming", it must be reported "immediately" and clinical investigation discontinued or modified until the finding is adequately evaluated and a decision is reached that it is safe to proceed. 21 CFR 312.1(a)(6).

The results of drug testing are critical not only to establish the basic safety and effectiveness of the product, but also to identify possible side effects, contraindications, and the need for special warnings, all of which must be included in the drug labeling. The sponsor of every new drug submits proposed labeling for FDA approval at the time of initial marketing and thereafter to reflect new information resulting from its use.

B. *Food Additive Petitions.* The Act also provides for FDA approval of food additives. Approval of an additive is codified in a regulation prescribing conditions under which the additive may be safely used. The regulation is promulgated solely on the basis of a manufacturer's petition, filed pursuant to 21 U.S.C. 348(b), which contains reports of studies establishing the safety of the additive. As with investigational drugs, the FDA does not perform safety tests on food additives; it must rely upon the data developed by the petitioner. Studies supporting a petition are ordinarily performed only on animals; human testing is uncommon.

The major purpose of the food additive provisions, added to the Act in 1958, is to prevent the unrestricted marketing and consumption in human food of chemicals without reasonable proof that these chemicals will not adversely affect man, either immediately, over a life-time or in the next generation.

C. *Monitoring Test Integrity.* Reports of studies submitted to the FDA as part of INDs or NDAs and food additive petitions must be complete, balanced and truthful if the Agency is to fulfill its duty of assuring that these products are safe and that new drugs contain accurate labeling based on the result of preclinical and clinical testing.

The FDA has not routinely monitored the conduct of animal test results submitted in support of either new drugs or food additive petitions. The reliability of the testing is normally checked by FDA review of the sponsor's reports of the underlying raw data. If necessary, the FDA may review the underlying raw data itself in the possession of the sponsor. The FDA may also select manufacturers or preclinical testing laboratories for routine surveillance inspections. When there is reason to believe that there are irregularities or discrepancies in the conduct of tests or the reporting of test data, the FDA may conduct a compliance inspection in order to evaluate the testing facilities, practices, and record keeping procedures to resolve any apparent discrepancy between the raw data and the report or to determine the truthfulness of data presented in the report.

Recent FDA experiences have identified significant problems in the manner in which

many preclinical laboratory studies are performed. Deficiencies in the quality and integrity of reported data have prompted the Commissioner of Food and Drugs to establish a biosearch monitoring program, and to propose the promulgation of good laboratory practices regulations which will delineate proper procedures for conducting preclinical laboratory studies. Congress has increased FDA's budget for the fiscal year 1977 by \$18.6 million specifically to help achieve the goals of the new program.

#### II—THE SEARLE INVESTIGATION

The genesis of the investigation of studies conducted by and for G.D. Searle was the FDA's discovery in 1972 of certain discrepancies in Searle data submitted in support of a large-selling anti-infective drug Flagyl. FDA review of the data was initiated because independent investigators had reported evidence that Flagyl was a carcinogen (an agent capable of producing cancer). Searle's own long-term toxicity study, submitted in 1970, had not concluded that Flagyl was a carcinogen. In April 1974, Searle submitted more studies on the issue of Flagyl's carcinogenicity and also submitted corrections to the data from its original long-term study. These corrected data raised further questions, resulting in FDA inspections initiated at Searle beginning in May 1974 and proceeding intermittently until the first of July 1975. These initial inspections failed to satisfactorily resolve questions of discrepancies and inadequacies in Searle preclinical testing and reporting of test results.

On July 23, 1975, Dr. Alexander M. Schmidt, then the Commissioner of Food and Drugs, established a special internal Task Force to review the conduct of animal experiments conducted by and for G.D. Searle and report to him. Inspections were conducted at Searle and at three independent laboratories, Hazelton Laboratories, Vienna, Virginia, The Wisconsin Regional Primate Center, Madison, Wisconsin, and Microscopy for Biological Research, Albany, New York, which had conducted or participated in the evaluation of animal studies for Searle.

The Task Force reviewed inspection reports covering 25 separate studies on seven different products, totaling approximately 500 pages plus 15,000 exhibits. Based on this information, data originally submitted by Searle, the scientific evaluation of animal tissue slides and other raw data, the Task Force issued its report to the Commissioner on March 24, 1976. A copy of the Task Force report was forwarded to the Consumer Affairs Section, Antitrust Division, Department of Justice, and to your office in April. Among other observations, the Task Force questioned Searle's handling of data applicable to the drug Aldactone and the reporting of studies on the food additive Aspartame.

The Task Force report was provided to Searle and the firm requested an opportunity to submit a written reply and to meet with the Commissioner to respond to the conclusions and recommendations of the Task Force. The meeting was held on May 18; Searle submitted its written reply to the Task Force report on May 21. I am enclosing a copy of the transcript of the May 18 meeting and the written reply of Searle to the Task Force report (Exs. 1a, 1b). At the meeting, Searle requested an opportunity to make further written reply to two memoranda by FDA pathologist M. Adrain Gross, a Task Force consultant who had reviewed much of the Searle preclinical testing data. This Searle reply was sent to the Agency on June 21, 1976.

#### III—INFORMAL ADMINISTRATIVE HEARING

After review in my office and in the office of the Associate Commissioner for Compliance of all the material relating to this matter, on September 3, 1976, the Agency issued, pursuant to 21 U.S.C. 335, a Notice of Hearing to G.D. Searle and Company, and \* \* \* for apparent violations of the Federal Food, Drug, and Cosmetic Act and related violations of 18 U.S.C. 1001 concerning Aldactone and Aspartame. The hearing, originally scheduled for September 21, 1976, was postponed at the request of Searle until October 20. An amended Notice of Hearing, dated September 15, 1976, was issued to correct an inadvertent omission from the earlier notice and to verify October 20 as the hearing date. A copy of the Notice of Hearing was forwarded to the Consumer Affairs Section and to Assistant United States Attorney Fred Branding of your office.

At the October hearing, Searle submitted lengthy written replies to the 305 Notice. Copies of these are enclosed. In addition, Searle reiterated a request for the Agency's investigational file covering the apparent violations which were the subject of the hearing. This request was denied, as was an earlier Searle request for "discovery" which referenced the Jencks Act, the Federal Rules of Criminal Procedure and *Brady v. Maryland*. Copies of correspondence concerning these requests have been provided to the Consumer Affairs Section and Mr. Branding.

As you know, preliminary reports of discrepancies in preclinical testing conducted by and for Searle were partially responsible for hearings on drug-related research held before the Senate Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practices and Procedures of the Committee on the Judiciary both chaired by Senator Edward Kennedy on July 10, 1975. Subsequent testimony updating the investigation and the positions of the FDA and Searle were taken before the joint subcommittees on January 20 and April 8, 1976.

#### IV—FAILURE TO SUBMIT SAFETY DATA ON ALDACTONE

**A. The Drug.** Aldactone is a new drug marketed by Searle pursuant to NDA 12-151. The drug was first approved in 1960 for use as a diuretic (an agent that increases the secretion of urine) for congestive heart failure and for hyperaldosteronism, a relatively rare but severe disorder of the adrenal cortex often resulting in a marked increase in high blood pressure. By 1974, Aldactone and a related drug utilizing the same active ingredient, Aldactazide, constituted approximately — of Searle's total pharmaceutical sales, approximately — a year. Current sales are reported to be — a year.

In 1963, Searle submitted IND 714 to conduct studies to develop data for the use of Aldactone in massive doses in the treatment of myasthenia gravis (serious muscular paralysis). In 1969, Searle amended its IND to cover testing of Aldactone for severe congestive heart failure at dosage levels much higher than those approved in the NDA.

**B. The MBR ("Mauro") Report.** In 1970 Searle designed two 78-week toxicity studies in the rat on Aldactone, one to support the long-term use of the drug at dosage levels approved in the NDA and the other to support higher dose levels in the treatment of severe congestive heart failure. The first study, later extended to 104 weeks in duration, was conducted by Hazelton Laboratories Vienna, Virginia; the second was performed by Searle in its own laboratories. The study conducted at Searle began in August 1970 and rates were sacrificed and

necropsied (autopsied) during February and March 1972.

In November 1972, consistent with prior practices, Searle submitted the slides of sections of organ tissues of the rats from the study it had performed to an outside consultant pathologist for examination. The slides were examined by Dr. Jacqueline Mauro, a board certified pathologist, at Microscopy for Biological Research, Ltd. Albany, New York (MBR). The report of her "readings"—the MBR report—was submitted to Searle on March 21, 1973. In a letter to MBR dated June 1, 1973, Dr. — acknowledged receipt of the report which "looks just fine."

In the summary of the MBR report, Dr. Mauro stated that her pathology review of the data suggested a group relationship, meaning a drug-related or drug-induced relationship, with tumors (adenomas) of the testes and liver. She also noted a significant number of thyroid tumors and non-tumorous thyroid lesions which she called "adenomatous goiter". Dr. Mauro recommended that these findings be measured for statistical significance. A statistical review of pathology findings is important since an absolute cause-and-effect relationship usually cannot be established in experimental biology. Therefore, an association between an agent and an effect is determined as a probability. If the incidence of a toxic response, such as a lesion, is found among animals treated with the agent under study to a significant degree greater than in animals not exposed to the agent, the established practice is to regard the agent as responsible for that toxic reaction. Where, as here, the toxic reaction is the development of tumors, it is likely to result in restrictive labeling imposed by FDA or even revocation of marketing approval.

**C. Searle's Reaction to the MBR Report.** In early August 1973, a statistically significant relationship between the administration of Aldactone and liver and testicular tumors, as well as thyroid tumors, was confirmed by Searle's Mathematics-Statistics Department based on the MBR report. Thereafter, at the request of —, some of the liver tissue slides were reviewed by a then recently hired Searle pathologist Dr. Rudolf Stejskal. He concluded that Dr. Mauro's analyses were "incorrect" and thus "unreliable" since certain slides which she had diagnosed as revealing benign tumors (adenomas) were, in his opinion, lesser lesions (hyperplasia) and that other slides that she had diagnosed as being benign tumors were in fact malignant tumors. On the basis of Dr. Stejskal's limited review of the liver slides, Searle did not submit the MPR report to the FDA.

In April or May 1974, Dr. Stejskal reviewed more of the slides which had been analyzed in the MBR report. This time, he felt that the slides revealed more thyroid tumors than had been reported by Dr. Mauro. Thus, while having concluded that her characterization of the liver slides was too extreme, he also found that her characterization of the thyroid lesions was too restrained. In various interviews with FDA personnel and in written submissions to the Agency, Dr. Stejskal has never commented on the MBR diagnosis of testicular tumors which, according to Searle's Mathematics-Statistics Department, were, as Dr. Mauro suggested, drug-related and statistically significant.

In August 1974—sixteen months after it received the MBR report—Searle sent the same slides examined by Dr. Mauro, and approximately 1,000 additional slides from the same study, to another contract pathologist, Dr. Donald A. Willigan. His report was re-

ceived by Searle in December 1974. It reveals a statistically significant drug-related increase in tumors of the thyroid and testes, as did the MBR report, but most important to Searle, not tumors of the liver. The concern at Searle over the liver pathology of the MBR report must have been particularly acute; undoubtedly the firm recognized that this information would have to be included in the Aldactone labeling, with a probable decrease in sales. The production of tumors in the testes and thyroid of the test animals, at statistically significant levels, must also have been unwelcome news but, insofar as Aldactone is felt to be active in these endocrine glands, Searle was prepared to argue that these tumors would be less likely to concern the FDA and the prescribing physician. We disagree with Searle's discounting the tumors of endocrine glands. However, the liver findings were more alarming because there was no theory upon which they could be discounted. Thus, unlike the MBR report, the Willigan report was submitted to FDA promptly upon receipt at Searle.

Immediately after the first Congressional hearings and the Commissioner's establishment of the Task Force, and immediately prior to the initiation of inspections by the FDA Task Force, which Searle had every reason to believe would include studies on Aldactone, Searle finally disclosed the MBR report to the FDA in July 1975, some 27 months after it had been received.

D. *Violation of 21 U.S.C. 331(e) and 18 U.S.C. 1001.* The FDA regards the MBR report as containing "alarming findings", namely, statistically significant drug-related tumors of the liver and also of the thyroid and the testes, especially given the wide use of the drug in humans. Accordingly, Searle was required to report these findings to the Agency "immediately" pursuant to 21 CFR 312.1(a)(6). If one were to conclude that these findings were not "alarming", they unquestionably were of the type that suggested significant hazards, contraindications, effects and precautions pertinent to the safety of the drug and therefore should have been submitted to the Agency "promptly" as also required by 21 CFR 312.1(a)(6). Even if one took the view most favorable to Searle that these findings were neither alarming nor suggestive of significant precautions, they were significant and thus were required to be submitted to the Agency at least within one year of receipt by Searle, 21 CFR 312.1(a)(5).

The primary purpose of the requirement that test findings be submitted to the FDA promptly is to permit the agency to assess for itself whether the investigational exemption should be modified or revoked. A manufacturer is not entitled to withhold damaging information in the hope that ultimately it might be proved incorrect. Moreover, the regulations do not preclude a manufacturer from filing expert criticism along with or following the reported study. In short, under any view of the facts, Searle was not entitled to discount the entire MBR report on the basis of Dr. Stejskal's review of some of the slides for only one of the tissue types. Moreover, to give great weight to Dr. Stejskal's analyses is to conclude that in May 1974 Searle had reason to believe, based upon his subsequent review of more of the slides, that administration of Aldactone in the study had caused even a greater number of thyroid tumors than reported by Dr. Mauro.

21 U.S.C. 331(e) prohibits the failure to make any report required by regulations under the IND provisions of the Act. The decision not to submit the MBR report was a conscious one and thus our Notice of Hearing charged this violation as an inten-

tional act under the felony provisions of the Act, 21 U.S.C. 333(b). Failure to submit the MBR report also constitutes concealment of a material fact, a violation of 18 U.S.C. 1001.

E. *Labeling of Aldactone: Violation of 21 U.S.C. 331(a).* When in March 1975 the FDA received from Searle the report of Dr. Willigan which confirmed the statistically significant incidences of thyroid and testes tumors reported to Searle two years earlier by Dr. Mauro, the Agency became concerned that the labeling for Aldactone was inadequate. On June 10, 1975, it convened the Cardio-Renal Advisory Committee, a group of non-FDA experts, to review the data then known on Aldactone. Even prior to the disclosure of the MBR report in July 1975, and based upon the result of the tissue slide examination by Dr. Willigan and the analysis at FDA's request of certain liver slides by Dr. John Boitnott, a pathologist at Johns Hopkins University, the Advisory Committee concluded that while the toxicological studies were incomplete they showed "definite and significant increases in neoplasia (tumors) of the thyroid gland, testes and possibly breasts and liver. They certainly warrant a warning to the medical profession and a curtailment in the recommendations for use." A copy of the Committee's report is enclosed. Aldactone has now been relabeled consistent with the Committee's views.

In view of the similar statistically significant thyroid and testes tumor findings in the MBR and Willigan reports, and the findings of liver lesions by both pathologists, we believe Searle's failure to submit the MBR report resulted in violation of 21 U.S.C. 331(a) for causing the shipment in interstate commerce of Aldactone which was misbranded within the meaning of 21 U.S.C. 352(a) in that its labeling did not reveal the potential of the drug to cause tumors, a potential disclosed by the MBR report. As you can see, the Advisory Committee's conclusion also supports FDA's view that the findings in the MBR report were "alarming".

#### V—ANALYSIS OF SEARLE'S EXPLANATIONS FOR FAILURE TO SUBMIT THE MBR REPORT

The administrative process, including the special Task Force and the 305 Notice and hearing, has been extensive; much of the dialogue between Searle and the FDA involves complex issues. The following portion of this letter, as well as parallel discussions of apparent violations involving Aspartame, must necessarily be specific in order to comprehensively and accurately reflect the context of this case. Regrettably, the length of this letter bespeaks our goal.

Searle's explanation for its failure to submit the MBR report, set forth in various documents, is best summarized in the firm's response to the Notice of Hearing which was submitted to the FDA on October 20, 1976. Without attempting to provide at this time a point-by-point critique of the Searle submission, comment upon the main recurrent themes provided in Searle's defense may be useful.

1. From the beginning, Searle has repeatedly taken the position that the MBR report was "proven" by its own pathologist to be "incorrect" and thus Searle was under no obligation to submit it to the Government.

Searle's contention that Dr. Mauro's pathology results were unreliable must be evaluated in light of the fact that pathology is a judgmental discipline. Proliferative lesions of the liver cells can be subclassified according to the particular nature of the proliferation. A diffuse increase in hepatocellular elements is usually termed "diffuse hyperplasia", or mostly, "hyperplasia". When such proliferation is not diffuse but rather a spotty distribution throughout the

tissues with islands or zones of proliferating cells, the term "nodular hyperplasia" is utilized. When such nodules of hyperplasia contain cells which the pathologist deems as having been permanently altered or "transformed" into neoplastic or tumor cells, the term "neoplastic nodule" is applied; this is taken to represent a group of proliferating cells which have "crossed the boundary" on the way to becoming a liver tumor. Various pathologists utilize other recognized terms such as "adenoma" to signify a benign liver tumor. A tissue slide characterized by one pathologist as an "adenoma" would also meet the criteria for "neoplastic nodule". The most extreme form of cellular proliferative stage, the malignant tumor variety, is commonly termed "hepatocellular carcinoma".

What is important, however, is that all these various terms represent a series of characterizations of stages of the proliferative process which can be viewed as a continuum. It is entirely possible that two pathologists may examine a given lesion and characterize it somewhat differently. This does not necessarily mean that one is "right" and the other is "wrong". Therefore, one must examine characterizations of liver alterations in a set of animals and ask whether a pathogenic process, such as a proliferative change, is evident.

Accordingly, it is proper to focus on the similarities among pathologists rather than emphasize the differences among them. When Dr. Mauro refers to "adenomas" and Drs. Stejskal and Willigan reference "nodular hyperplasia" and Dr. Robert Squire, a cancer expert at the National Institutes of Health who reviewed some of the liver slides at the request of the FDA Task Force, talks about "neoplastic nodule", each one is calling attention to a proliferative change in the liver. One may grade such a proliferation along the continuum or by different phrases from another one, but basically they imply the same problem. The proclivity of experts to use different terms in liver pathology was recently demonstrated at a workshop at the National Cancer Institute published in "Cancer Research", Vol. 35, Nov. 1975.

Searle also alleges "extreme variation and contraindications in diagnosis" between Drs. Stejskal and Willigan on the one hand and Dr. Mauro on the other. FDA believes that the differences in diagnoses were not extreme and reflect merely the continuum of diagnostic evaluations of the same class that are well recognized in the field of pathology.

2. Searle argues that the IND regulations presuppose that the data which must be submitted must be accurate and reliable. 305 Reply, pages 10, 15. 21 CFR 312.1(a)(6) refers only to "findings" which are significant or alarming. Accuracy is not used as a standard precisely because such findings at this preliminary stage may, in many cases, be undetermined. By contrast, the requirement to submit progress reports within a year does state they be "accurate", reflecting the Agency expectation that by then any discrepancies will have been resolved.

Searle argues that the applicable statute and regulations do not require reports of all animal studies conducted during the course of clinical investigations but only reports of testing on humans and of those animal tests conducted before human testing is initiated. In addition, Searle contends that the IND regulations are unreasonably ambiguous. These arguments are without merit.

In the interest of protecting patients taking experimental drugs, the statute authorizes regulations requiring the reporting of animal tests before tests on humans are

