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Mr. DOMENICI. I see no reason whatsoever. The President has twice sent the compact to the Congress and I would strongly resist any implication that he has not sincere in doing so. In the discussions with the administration leading to this resolution, the original assumption contained in the President's budget that funding would occur in function 150 in the Department of State was dropped by the administration. The assumption of this resolution is the same as has twice been agreed upon by the Budget Committee, and that is that funding for the freely associated states will continue in function 800 in the Department of the Interior. I can not conceive of the Department of the Interior, with the full support of the Office of Management and Budget, not transmitting the necessary supplemental in sufficient time for enactment prior to fiscal year 1986. I would like to commend the Senator for his strong support for the compact, and it is a tribute to him and also to the distinguished Senator from Louisiana, Senator JOHNSTON, that the compact has twice been reported unanimously to the Senate. I look forward to its early passage as reported by the committee and can assure the Senator of my full support in enactment of the necessary supplemental which the President will request.

SACCHARIN STUDY AND LABELING ACT AMENDMENTS OF 1985

The PRESIDING OFFICER. Under the previous order, the hour of 4 p.m. having arrived, the Senate will turn to the consideration of S. 484, which the clerk will state by title.

The assistant legislative clerk will read as follows:

A bill (S. 484) to amend the Saccharin Study and Labeling Act.

The Senate proceeded to consider the bill which had been reported from the Committee on Labor and Human Resources, with an amendment:

On page 2, line 3, strike "1985", and insert "1987".

So as to make the bill read:

S. 484

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled. That section 3 of the Saccharin Study and Labeling Act (21 U.S.C. 348 nt.) is amended by striking out "During the period beginning on the date of enactment of this Act and ending twenty-four months after the date of enactment of the Saccharin Study and Labeling Act Amendment of 1983" and inserting in lieu thereof "During the period ending May 1, 1987".

Mr. HATCH. Mr. President, I bring to the floor for final consideration S. 484, which extends the Saccharin Study and Labeling Act for 2 years. It is subject to a time agreement worked out between myself and the committee majority.

The Labor and Human Resources Committee ordered the bill reported on April 17, 1985 without opposition.

The Saccharin Study and Labeling Act was passed in 1978 in response to a proposal by the Food and Drug Administration to remove saccharin from the market. This proposal followed a study report implicating saccharin in increased bladder tumor incidence in rats. At that time saccharin had been in use as an artificial sweetner for over 80 years and had never been causally linked to any illness or death in humans. It was an important factor in the physical and emotional health of diabetics and others who need to control their weight or caloric intake.

The FDA proposal prompted considerable congressional interest. After pursuing its own inquiry, Congress felt that the evidence at that time was insufficient to conclude that saccharin was a significant health risk in humans, and found that it conferred real benefits on a significant portion of the population. Congress response was the Saccharin Study and Labeling Act, which forbade FDA from moving against saccharin solely on the basis of data available when it was enacted. This step clearly conveyed to FDA Congress' intent that the agency have more solid and substantial evidence of a human health risk before it restricted or eliminated the use of the sweetener.

Despite the passage of 7 years, the essential conditions have not changed, thus S. 484's extension of the act is completely appropriate. Specifically, though several important studies have been completed since that time, no scientists at the hearing on the bill felt that saccharin has been demonstrated to be a significant human health risk or that the current evidence warrants its removal from the market. Additional studies are currently underway to try to determine saccharin's mechanism of action in humans. But 7 years after passage of the original act, there is still no evidence that saccharin is a carcinogen in humans, despite an unusually long marketing history. And the Commissioner of the Food and Drug Administration testified:

(A)s in the past, we still do not adequately know the answer to all of the questions and uncertainties giving rise to the original 1977 saccharin moratorium. The actual risk, if any, of saccharin to humans still appears to be slight, however.

Further, saccharin's importance to the health of diabetics and others, while somewhat diminished in several applications by the availability of aspartame, remains significant. Thus, the American Diabetes Association and the Juvenile Diabetes Foundation, among others, support the extension.

I note in conclusion that the so-called moratorium in the Saccharin Study and Labeling Act is not absolute, but simply imposes certain limitations on regulatory action against the sweetener. Should information come available during the next 2 years demonstrating a public health risk from continued use of saccharin, under S. 484 the FDA retains the authority to take regulatory action.

Thus I have no hesitation in asking my colleagues to support this bill. It is a bipartisan bill, and it is passed out of committee without an opposing vote.

We have agreed to a time agreement on this bill with one amendment.

Mr. President, I reserve the remainder of my time.

Mr. KENNEDY addressed the Chair.

The PRESIDING OFFICER. Who yields time?

Mr. METZENBAUM. Mr. President, I yield the Senator time.

Mr. KENNEDY. Mr. President, I support this bill to extend the Saccharin Study and Labeling Act.

Saccharin is an important part of the diets of many Americans who need to avoid sugar intake. It is particularly important for diabetics.

While some things have changed in the artificial sweetener field since the last extension of this legislation—including the development of aspartame and new studies suggesting cyclamates may not be carcinogenic—there does not appear to be a fully satisfactory substitute for saccharin currently available.

The committee hearings we held reinforced my belief that an extension of the saccharin ban moratorium is appropriate at this time.

Senator METZENBAUM will be offering an amendment to require quantity labelling of aspartame in soft drinks. While the FDA has found aspartame to be generally safe, the center for disease control has recommended that further tests of aspartame be conducted to determine whether some groups may suffer harmful effects from aspartame consumption—particularly at high dose levels.

Our committee report mandates that these tests occur. It seems to me appropriate that consumers should be able to monitor their own consumption of aspartame.

Mr. President, I hope that the Members of this body will support Senator METZENBAUM's amendment to insure that the consumers of this country would be able to make that determination in terms of their own consumption.

Mr. President, on the bill itself, was there not time yielded to the Senator from Massachusetts?

The PRESIDING OFFICER. I did not catch the request of the Senator from Ohio.

Mr. KENNEDY. On the bill itself, is not the time divided between the Senator from Utah and the Senator from Massachusetts?

The PRESIDING OFFICER. It is divided between the Senator from Utah and the Senator from Ohio or their designee. I did not catch how much time the Senator from Ohio yielded.

Mr. KENNEDY. I thank the Chair.

Mr. METZENBAUM. Mr. President, I appreciate the support of the distinguished Senator from Massachusetts, whose record in the field of health legislation is second to none in this Congress. We have before us the bill to extend the period of exemption from the Delaney Act for the continued use of saccharin. I supported that extension because the distinguished chairman of the committee was kind enough to set a hearing not alone on the issue of saccharin but on the issue of saccharin and other sweeteners, including cyclamate and aspartame.

Out of that hearing, the Committee concluded that there should be an extension of the saccharin exemption, not for 3 years but for 2 years. In addition, the Committee provided that the Food and Drug Administration must report to the Congress on how the label laws for saccharin are being observed. It is a fact that some companies are complying with the law while others are not. For others it is a question of degree—some labels are in typeface so tiny that it is almost impossible to read.

The real issue that we have before us here today, Mr. President, relates to the aspartame labeling amendment which I shall shortly send to the desk. What this amendment would do is amend the Saccharin Study and Labeling Act to provide that any soft drink which contains aspartame shall state the total number of milligrams of aspartame contained in such serving of such soft drink.

I want Members of this body to understand where we stand on this issue. I shall not raise my voice during this debate. I shall not implore Senators to vote for my amendment. I shall ask them only to consider the merits of the issue. If they consider the merits of the issue, then they have to vote for the amendment because, on the merits, people have a right to know how much aspartame is in the product that they are drinking. That is all.

Nobody is saying that consumer cannot use aspartame. I point out to my colleagues that, as a matter of fact, the National Soft Drink Association, the organization that represents all of the soft drink people, at one point was prepared to take a position totally opposed to the use of aspartame in soft drinks. They never took quite that position as I shall discuss later.

Mr. President, if this amendment passes, the industry will have 18 months to implement its provisions. We are willing to give the industry adequate time to make the changes on the cans so that people may learn what is in the product that they are ingesting.

Mr. President, let me at the beginning deal with a prevalent misconception about this amendment. Lobbyists have been on the telephone, scurrying around all over the Hill, calling Members of this body, telling everyone that this amendment will, in some way, injure the bill. They have indicated that there is an urgent need for the saccharin extension and that my amendment will slow the bill down and even kill it.

I want Members of this body to understand that that claim is totally absurd. The FDA Commissioner, Dr. Young, testified at our hearing as follows:

I must emphasize that even if the ban were not extended, it would take a period of time for FDA to evaluate its action and then proceed through preliminary and final rulemaking which would be in itself, a couple of years' process . . . with the most rapid action it is 180 days to a year.

It appears my colleague, with whom I worked very well, the chairman of the committee, wrote a letter on this subject. He indicated in that letter that the attachment of my amendment to this bill would jeopardize the bill's fate in the House. I thought that was an important statement for him to be making, so I called the distinguished chairman of the House committee having jurisdiction over this matter.

I am pleased to report to my colleagues that he does not confirm that it would cause delay. Actually, he said that until he knows what the amendment specifically provides, he is hardly in a position to make any such indication. However, there is certainly no indication that it would kill the bill.

Mr. SIMON. Would my colleague yield for 1 minute?

Mr. METZENBAUM. I do indeed yield.

Mr. SIMON. I thank him for yielding.

Mr. President, I think the point he made a moment ago needs underscoring. He mentioned lobbyists contacting Members of the Senate on his amendment. They were contacting on the basis that he had a 6-month time limitation. In fact, with that 18 months, there should be no difficulty for any bottler to accommodate to this reality. It just seems to me that the Senator's amendment can do no harm and very well may do some good in safeguarding the people of this country, particularly some who may have some very real problems with this particular ingredient.

Mr. METZENBAUM. Mr. President, I very much appreciate the comments and the support of my friend and colleague from Illinois. I have no reservation in saying that, indeed, at one point, we were contemplating 6 months.

The Senator from Illinois had indicated his concern about that being too short a period of time. I agreed with the Senator's contention, and therefore I put in the 18-months figure. However, the issue is not so much how long the industry will have to implement the amendment. The issue is can we prevail upon the industry to disclose how much aspartame is in the can or the bottle?

Mr. SIMON. I thank the Senator from Ohio.

In his leadership on this matter as in many others, I have referred to him, half in jest and half not in jest, as the tiger of the Senate. He is that. He gets hold of an issue and fights for the cause. He has been fighting for the health of the people of this country. I commend him, and I am pleased to support his amendment.

Mr. METZENBAUM. I appreciate the support of the Senator from Illinois, who has served well and with distinction in the Congress of the United States, and we are happy to have him in this body.

Mr. President, I should like now to get to address the substance of this issue.

During the committee hearing, we had an aspartame scientific panel as well expert FDA testimony on aspartame. Aspartame issues were examined in extensive detail. This amendment evolved from that hearing and I would now like to offer three basic reasons for its passage.

Reason No. 1 is the consumer's right to know. People have a right to know about the makeup of the products they consume. It is no secret that the distinguished Senator from Florida [Mrs. HAWKINS] and I have a bill pending which has to do with the labeling of products generally.

Reason No. 2, the FDA as well as doctors around the country have received hundreds of complaints from people who believe that they have had adverse physical reactions to NutraSweet.

Professor Wurtman of MIT made a very strong case at the hearing for quantity labeling, on the basis that physicians treating these complaints would at least know how much has been consumed. They will be able to take into consideration, in making their diagnosis, whether the taking or the use of aspartame was a factor.

Professor Wurtman also argued that those with symptoms who consumed large amounts of NutraSweet will be able to gauge their consumption, and those who think they have symptoms but in reality have consumed only small amounts of NutraSweet would be able to stop worrying.

Third, significant medical and safety questions have been raised about NutraSweet, and I will get into some of those questions as we proceed in the debate this afternoon.

Clearly, we need to provide people with more information about this product than they already have. With respect to the criteria of aspartame or NutraSweet safety, the food and safety law is clear. The Government does not have to prove that a particular food additive or artificial sweetner is harmful. The Government does not have that burden of proof. The manufacturer must prove that it is safe and that there is reasonable certainty that no harm will result from its use.

I should like to share with my colleagues the history of NutraSweet. In

1977, the Food and Drug Administration recommended that Searle—it is their product—be brought before a grand jury, on the basis that its testing procedures were irregular and that false statements were made. It was the FDA that made that recommendation. These tests included many of the key NutraSweet tests.

In 1980, a public board of inquiry recommended that NutraSweet not be approved until further tests on brain tumors could be dealt with. The FDA Commissioner rejected that finding and approved NutraSweet. I will return to that issue at a later point in the debate.

At the hearing, we referred to in-house FDA memos which showed that three of the six FDA scientists advising the Commissioner, the so-called Commissioner's team, recommended that NutraSweet not be approved because certain tests were still dubious. We have, in addition, the concern expressed by Dr. Wurtman about the effects on brain chemistry of aspartame, concerns which the Soft Drink Association itself cited in its draft objection to NutraSweet in 1983. I will return to that draft objection of the Soft Drink Association subsequently, as well.

Clearly, questions surround this product.

In addition to those questions having to do with the testing and approval of NutraSweet, there is also the issue of the ADI for NutraSweet, or the acceptable maximum daily intake.

I should like to quote from an FDA memorandum dated January 8, 1983:

> The Bureau of Foods had previously evaluated the results of data from an extremely comprehensive animal testing program and established the acceptable maximum daily intake, the ADI, for aspartame to be 20 milligrams per kilogram of body weight per day. This figure is based on application of a hundredfold safety factor to the no-effect dose, 2,000 milligrams per kiligram, in a chronic rat study.

What does that mean? It means that the FDA normally applies a hundred fold safety factor to regulated food additives. In the case of aspartame, they made an exception. They increased the ADI to 50 milligrams per kilogram, and they said they had the tests to prove that this could be done safely.

What does an ADI really mean.

What an ADI means is this: If you weigh 150 pounds, you would have to drink 17 cans of diet soda with 100 percent NutraSweet to hit the acceptable maximum daily intake.

I do not really believe that many people drink 17 cans of diet soda with 100 percent NutraSweet and hit the ADI. However, if you are a child weighing 25 to 30 pounds, you would hit that limit with three or four cans of soda. That is not something that is going to happen to all kids. But certainly large numbers of children are likely to consume NutraSweet at these levels.

Nobody is saying that someone is going to keel over if they exceed the ADI on a given day. But with all the concerns raised about the safety of NutraSweet, does it not make sense, is it not logical, for individuals and their physicians to know how much NutraSweet is in the diet soda?

What could be so terrible about stating the amount? How else will the user or the physician know if the person is exceeding reasonable consumption limits, particularly during the summer months?

Some would say, "Well, even if we told them the amount, they wouldn't understand." Some would. Some would not. But what in the world is so horrific? What in the world is so terrible? Why is it such a problem for the industry, within 18 months, to change their cans to indicate the amount of aspartame—that is NutraSweet—in the product?

Some would say, "Why label only soft drinks?" The answer to that is soft drinks are the major source of NutraSweet consumption.

Those who argue against the amendment on the basis that it singles out soft drinks are very quick to point out that they do not support labeling of any products containing NutraSweet.

Besides, if we mandate labeling of soft drinks, do you not think the other manufacturers will get the message and seriously consider implementing their own labeling?

Some would argue—and it has been stated—"Why don't you indicate how much sugar there is on the label?" As a matter of fact, if somebody cares to offer an amendment or to suggest such labeling, I would have no problem with that. I am one who firmly believes that the more the individual is able to know about the food he or she consumes, the better chance that individual has in seeing to it that the food ingested by him or her will be healthful and not dangerous to his or her life.

Dr. Roberts, of the National Soft Drink Association, testified at the hearing and said if a consumer wants to know how much NutraSweet is in a can of diet soda, they can write the National Soft Drink Association in Washington to find out. He said:

> We like people to have this information so we have no objection whatsoever, and, in addition, we try to provide additional information by putting our associated kinds of brochures.

So they are saying, "You can get the information, we are willing to give it to you, we might even make up a brochure, but we don't want to put it on the can."

Why? Is it that there is no room on the can? Is it that the people are just too nosy, to find that out?

I went to a can of Diet Coke to see what was on the can. Mr. President, they have enough reading material on the can to fill the CONGRESSIONAL RECORD.

On the front label they say, "100 percent NutraSweet brand sweetener." They say, "Saccharin-free, low-calorie cola: "phenylketonurics," contains "phenylalanine."

Let us take a look at the back of the Diet Coke label.

Nutrition information per serving

Serving size (ounces)	6 oz.
Servings per container	2
Calories per serving	0
Protein	0
Carbohydrate	(*)
Fat	0
Sodium (milligrams)	35

* Less than 1 gram.

And it continues on. They have a lot of material on the back of that label.

Perentage of U.S. recommended daily allowances (U.S. RDA): contains less than 2 percent of the U.S. RDA of protein, vitamin A, vitamin C, thiamine, riboflavin, niacin, calcium, and iron. Contains carbonated water, caramel color, aspartame, (NutraSweet brand), phosphoric acid, potassium benzoate preservative, natural flavors, citric acid, caffeine.

That is not all. It has more on the back label. "NutraSweet and the NutraSweet symbol," says the back label, "are the trademarks of G.D. Searle & Co. Consumer information: call 1-800-GET-COKE," and then the number "438-2653."

Well, I guess it would not be too much of an imposition for the soft drink industry to indicate that there are 180 to 200 milligrams of NutraSweet in that can of Diet Coke. It would not ruin the can or its appearance.

Now, the Soft Drink Association has also said that if consumers want to know how much aspartame is in a can of Diet Coke, they can call the number on the can; 1-800-GET-COKE.

Now, my staff did just that. At 9:09 a.m. on May 1, my staff called the Coke consumer information line, 1-800-GET-COKE, and after listening to a jingle, the operator came on the line. She was a very nice woman. Her name was Pat. My staff asked her the following question: "Can you tell me how much NutraSweet is in the can?" Her reply, "No. I'm sorry, I don't have that information." My staff then asked, "Is there any limit to the amount you should consume?"

Reply: "No. You can drink 40 cans a day." My staff asked her about kids. Could they drink that amount? Her reply, "No problem."

Now, FDA's acceptable maximum daily intake for a 150-pound person is 17 cans, and for a 25- to 30-pound person, 3 to 4 cans.

So I say that dialing 1-800 GET-COKE does not get you very far in obtaining information on how much NutraSweet is in a can of Diet Coke. Would the Chair be good enough to advise how much time the Senator from Ohio has remaining?

The PRESIDING OFFICER. The Senator has 32 minutes remaining.

Mr. METZENBAUM. I thank the Chair.

I ask my colleagues to keep in mind that the soft drink association, which is strongly opposed to letting consum-

ers know how much NutraSweet they are consuming, is the same association which in 1983 prepared a draft legal document objecting to NutraSweet ever being allowed on the market, citing serious and unresolved questions about the public health.

Let me explain the significance of that statement. The National Soft Drink Association, along with the law firm of Patton, Boggs & Blow, prepared a document that was to be submitted before the U.S. Department of Health and Human Services, Food and Drug Administration. The document was entitled "Objections of the National Soft Drink Association to a Final Rule Permitting the Use of Aspartame in Carbonated Beverages and Carbonated Beverage Syrup Bases and a Request for a Hearing on the Objections." The issue before the Food and Drug Administration at that time, according to this draft objection was aspartame; food additives for direct addition to human food. 48 Federal Register 31376, July 8, 1983.

I want to explain to my colleagues that the draft legal document was not filed, but it was prepared and I ask unanimous consent that at the conclusion of my remarks the entire contents of that draft objection be included in the RECORD.

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

(See exhibit 1.)

Mr. METZENBAUM. Although it was not filed, that does not mean that it was not the position of the organization at that time. It does not mean that the findings and the conclusions reached in that document were not valid. It only indicates that for reasons best known to them, unquestionably business reasons, they decided not to file it.

But they were not objecting to labeling, which is all that my amendment would do. My amendment would only indicate the amount of aspartame that is in the product.

Their objection took the position that aspartame should not be included in soft drinks. That draft objection indicates that the organization had significant health concerns with the product before it was approved for soft drinks.

Let me direct your attention to some of the things that they said in that draft document:

G.D. Searle and Company has not demonstrated to a reasonable certainty that the use of aspartame in soft drinks, without quantitative limitation, will not adversely affect human health as a result of the changes such use is likely to cause in brain chemistry and under certain reasonable anticipated conditions of use.

For these reasons, Searle has not met its burden of demonstrating to a reasonable certainty that the unlimited use of aspartame, especially in combination with carbohydrates, will not adversely affect human health.

It went on to say that:

The questions posed by Dr. Wurtman are significant because of the seriousness of the potential effects E.G., changes in blood pressure and because of aspartame's anticipated widespread use—one that includes consumption by potentially vulnerable subgroups, such as children, pregnant women, and hyperactives.

They went on to say in that document:

Specifically, Searle has not met its burden under section 408 . . . to demonstrate that aspartame is safe and functional for use in soft drinks.

And they further stated:

Collectively, the extensive deficiencies in the stability studies conducted by Searle to demonstrate that aspartame and its degradation products are safe in soft drinks intended to be sold in the United States, render those studies inadequate and unreliable.

Now, the National Soft Drink Association in August 1983, thought that aspartame should not be used in soft drinks. But so many of my colleagues have been called recently and told that they should not vote for this amendment. Yet this amendment does not provide that the product should not be sold, only that the people who use the product have a right to know how much of it they are consuming.

Now, I think that it is important to know what occurred at the Department of Health and Human Services when aspartame was approved. I would like to share with my colleagues a memo dated May 19, 1981, from the Acting Associate Commissioner for Health Affairs on the subject of aspartame to the Commissioner of the Food and Drug Administration.

In this memo, they state the following:

The first and primary agenda item relates to the brain tumor issue. This was the point on which the Public Board of Inquiry concluded that safety had not been shown. A first draft "final decision" on this issue is attached.

They went on to say:

The major issue discussed at the hearing was the background rate for spontaneous brain tumors in the specific strain of rat used by Searle.

They talked about the conduct of the study.

The conduct of all three rat studies has been criticized by Dr. Olney. Some of the staff scientists believe the studies were adequately conducted, while others tend to agree with Dr. Olney that one or more of the studies was severely flawed. Again, the different positions are documented.

Mr. President, I ask unanimous consent that the FDA memo be printed in the RECORD at the conclusion of my remarks.

The PRESIDING OFFICER (Mr. GORTON). Without objection, it is so ordered.

(See exhibit 2.)

Mr. METZENBAUM. Now, Mr. President, my colleagues may go ahead and defeat this amendment. But I hope they will remember this debate in the months ahead. I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA's own scientists were split on the issue.

So what we are talking about is, do we agree that there will be labeling indicating how much aspartame is in the product or do we close our minds to all the questions surrounding this product and turn our backs on the consumer's right to know.

I am frank to tell you I stand on the floor and I do not have all the answers. But I believe that this body has some responsibility to the children, grandchildren, and adults who are consuming these soft drinks. And all I am asking for here today is that which I consider to be the very minimum. To tell the people who are drinking these diet sodas how much aspartame is in the product.

Now I might note that some have said that the Diabetes Association opposes this amendment. My staff spoke with their Washington representative today. They do not oppose this amendment. Their official position is to advise caution for pregnant women and children for both aspartame and saccharine consumption.

In conclusion, Mr. President—and I will confess that I have spoken at some length, but I speak at some length because I am concerned about what aspartame may do to people if ingested in too great quantities. I am concerned about the possibility of brain tumors and other forms of brain damage. Those who studied the issue at the FDA were concerned as well.

This amendment is basic. It is simple. It does not really ask for much, and for the life of me, I cannot understand why the Soft Drink Association has spent so much time and has done so much lobbying. What have they got to hide? All we are asking is how much aspartame is in the soft drink. And we are saying take 18 months, if you need that amount of time, in order to change your cans in order that we will not place an economic burden on your business.

My amendment is no big deal. It is not going to save the world. It is not going to solve problems in Nicaragua and it is not going to balance the budget. But it is one little step in the right direction. We will be providing people with the minimum amount of information they deserve about a substance which poses many unanswered questions about basic consumer health and safety.

Mr. President, I do not wish to delay the Senate with lengthy debate. I would like to submit for the record a number of scientific and other submissions relating to aspartame. I ask unanimous consent that they be printed in the RECORD.

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

[From the Washington Post, April 24, 1985]

SWEETENERS FACE SCRUTINY OVER SAFETY

(By Sally Squires)

Just in time for spring dieting, three artificial sweeteners—aspartame, saccharin and cyclamates—are in the news.

Last week, a Senate panel rejected an amendment requiring labeling on soft drinks containing aspartame. This week, Congress considers whether to keep saccharin on the market. Meanwhile a National Academy of Sciences committee is reviewing the health effects of cyclamates, which were banned in 1970 because of a possible link with cancer.

Despite growing scientific evidence that aspartame causes alterations in brain chemicals and may change behavior, the Labor and Human Resources Committee defeated an amendment requiring soft drinks containing aspartame to list the amount of the chemical on the package.

Aspartame, marketed under the trade name NutraSweet by G.D. Searle and Co., is used in a variety of foods and beverages, ranging from diet soft drinks to the table sugar substitute known as Equal. Products containing NutraSweet carry a label warning people with the genetic disease phenylketonuria (PKU) to avoid these food and beverages. PKU sufferers are born lacking an important enzyme that allows them to digest the amino acid phenylalanine—a building block of protein and an important constituent of NutraSweet. PKU infants who consume phenylalanine become severely brain-damaged, and thus must be placed on a restricted diet for the rest of their lives.

Studies in humans and in animals suggest that aspartame can cause changes in neurotransmitters—the chemical substances that send messages throughout the brain. These changes are particularly pronounced when aspartame is consumed with carbohydrates. Among the health effects associated with aspartame consumption are headaches and behavioral changes.

The FDA has established guidelines that suggest limiting aspartame consumption to 50 milligrams per kilogram of body weight. A kilogram is equal to 2.2 pounds. This means that a 25-pound child (about 11 kilograms) should consume no more than 550 milligrams of aspartame a day—about the amount in four cans of diet soda.

Without labels describing how much aspartame is included in a product, "it is difficult if not impossible for the patient or his physician to know how much aspartame he has eaten or drunk," Dr. Richard Wurtman, a professor at the Massachusetts Institute of Technology, reported at a recent hearing before the Labor and Human Resources Committee. "I doubt that one consumer (or physician) in a thousand now realizes, for example, that a can of Tab provides less than one fourth as much aspartame as a can of Diet Pepsi or Diet Coke."

"Although we've made some progress with further NutraSweet and saccharin tests, we still have not fully protected the health and rights of consumers," said the amendment's sponsor, Sen. Howard M. Metzenbaum (D—Ohio).

"I believe that it is essential that companies which include aspartame in their products be required to indicate on the labels how much of the sweetener is present in each can or serving," adds Wurtman, who says he uses aspartame himself. "I think that it would be very good to have labeling of all artificial sweeteners."

A spokesman for Searle said that the company is not "against labeling if it appears on all food products. We thought it would be unfair to single out just NutraSweet."

"It is a very safe product. NutraSweet is the most tested product on the market today."

Other recent scientific evidence suggests a link between the development of nonmalignant skin lesions and the consumption of aspartame. Research also suggests headaches and perhaps even high blood pressure can result from combing aspartame with certain medications.

One study, published in the Annals of Internal Medicine described how a 22-year-old woman who drank daily 36 to 44 ounces of an aspartame-sweetened diet drink developed skin lesions on her thighs. Controlled tests over a period of weeks documented that the woman's lesions disappeared and reappeared with the use of aspartame. Two other reports published earlier this year in the American Journal of Psychiatry and the British journal Lancet document behavioral changes among aspartame users.

Cyclamates could again become a choice for dieters and diabetics. A National Academy of Sciences committee is currently reviewing the scientific literature regarding the banned artificial sweetner—at the request of the Food and Drug Administration (FDA)—to help determine whether it causes cancer. The committee is expected to report its findings in June. If the scientific evidence is inconclusive, then the committee will design research that could answer the safety question of cyclamates once and for all.

Saccharin could soon be banned if Congress refuses to extend the most recent moratorium on prohibiting saccharin sales, which expired Monday. In 1977, despite evidence that saccharin caused bladder cancer in rats, Congress passed a law that allowed it to remain on the market. But FDA Commissioner Frank Young told a congressional committee recently that even if the moratorium is not renewed this week, it would take between six months and a year for saccharin to be removed from the market.

[From the Science Times, Feb. 5, 1985]

SWEETENER WORRIES SOME SCIENTISTS

(By Jane E. Brody)

As sales of aspartame, the nation's newest artificial sweetener, expand rapidly among millions of users, scientific concern is also growing among some researchers about its safety.

The researchers are alarmed by recent reports that a small percentage of users, including at least two young children, may have suffered severe adverse reactions to aspartame. Especially worrisome are reactions involving the brain, including seizures, incapacitating headaches, dizziness, behavioral changes and depression.

Although there is at present no evidence, there is concern, too, over the possibility that in some consumers, aspartame may cause subtle disruptions in the balance of brain chemicals that influence mood, alertness and hunger for certain nutrients. Animal studies have raised the issue but its investigation is only just beginning.

Two scientists, Dr. C. Keith Conners of Children's Hospital in Washington and Dr. Richard Wurtman of the Massachusetts Institute of Technology, believe that the Food and Drug Administration misled the public on aspartame's safety by understating the concern voiced in a recent official scientific analysis of consumer complaints.

"If you read the C.D.C. report," Dr. Wurtman said in an interview, referring to the national Centers for Disease Control, "it doesn't sound nearly so complacent as the F.D.A. Talk Paper that interpreted the findings for the public."

According to the C.D.C., its detailed investigation of 200 consumer complaints, out of more than 600 received, suggests the need for a systematic study of adverse effects, especially neurological and behavioral effects, which accounted for 67 percent of the complaints received.

"The number of instances of persons challenging themselves several times with aspartame-containing products and reporting symptoms with each rechallenge suggests that some individuals may be sensitive," the report states. "The only way to clearly determine this is through focused clinical studies." Citing the "subtlety and potential seriousness of some of the manifestations" reported by consumers, the disease control centers said the studies should concentrate on such symptoms as "headaches, mood alterations and behavior changes."

The manufacturer of aspartame, G.D. Searle & Company, said a proposal for a clinical study has been submitted to the F.D.A., but there are as yet no plans to actively monitor the effects of aspartame in the general population.

Searle says the C.D.C. findings are not surprising, given the fact that more than 100 million people now use aspartame. Dr. Gerald E. Gaull, vice president for nutrition and medical affairs for aspartame at Searle, said it is possible that "a few people may be allergic or sensitive to it." He added that "for those few people, the issue is not one of safety but rather of food selection."

Both the drug agency and Searle say aspartame is the most extensively studied food additive in history and that the studies clearly establish its safety. Dr. Gaull noted, "It's not just the F.D.A. that has viewed the tests as adequate, but also the World Health Organization and comparable regulatory agencies in Canada, the United Kingdom, Japan and about 37 other countries."

Dr. Sanford Miller, head of the F.D.A.'s Bureau of Foods, said: "I don't know of any substance in recent years that's been looked at with the intensity of aspartame. No one had yet come up with the slightest evidence to show we were wrong in approving it."

However, some researchers and consumer organizations assert that the studies have not been careful or far-reaching enough to establish the safety of aspartame, which is now entering the food supply at an unprecedented rate following its approval in 1983 for use in soft drinks.

For example, Dr. Walle Nauta, a Massachusetts Institute of Technology psychologist who heads a public board of inquiry that was asked by the F.D.A. in 1980 to review safety concerns about aspartame, has said that had the panel known how widely aspartame would be used, it would have issued stronger recommendations. He told Common Cause, a public affairs organization that completed a nine-month investigation of aspartame last year, that use of aspartame in soft drinks "never figured in our decision making."

Dr. Nauta's panel was also limited in its assessment to interpreting the results of safety tests. Whether the tests were properly conducted in the first place was not considered, he said.

FOUND IN WIDE VARIETY OF FOODS

Aspartame, marketed as Nutra-Sweet (when used as a food additive) and Equal (the table-top version), is now found in such foods as soft drinks, gum, breakfast cereals, mixes for hot chocolate and cold drinks and pudding mixes. Although in most products it is combined with either sugar or saccha-

n, a trend is already evident toward the se of aspartame as the sole sweetener in rocessed foods. Coca-Cola and Pepsi-cola, or—example, announced they would be sing it alone in diet soft drinks, and Ralston-Purina has just introduced a new ereal, Sunflakes, sweetened only with spartame. Several food processors have iled proposals to use the sweetener in ogurt, ice cream and flavored drinks.

Since it was approved for use in this country in 1981, worldwide sales of aspartame have grown from $74 million in 1982 to $800 million last year. It has been an enormous financial boost for a company that a decade ago was embroiled in costly controversy over the quality of its safety tests on several major drugs and aspartame.

Aspartame was originally approved for marketing in 1974, but the approval was quickly stayed when a scientist, Dr. John Olney of Washington University, and an attorney, James S. Turner, objected on the basis of Dr. Olney's findings in animals that aspartame might cause cancerous brain tumors. Dr. Olney remains a strong critic of aspartame approval. Mr. Turner, a consumer advocate with the Community Nutrition Institute in Washington, said the studies needed to clarify this risk had not yet been properly done. The institute recently petitioned the United States Court of Appeals for the District of Columbia to halt further marketing of aspartame products pending the outcome of a requested public hearing on aspartame's safety.

Nor were a number of key studies that had been called into question as scientifically lacking in design and execution ever redone, according to Common Cause and Mr. Turner. Nonetheless, in 1981, Arthur Hull Hayes, then Commissioner of Food and Drugs, approved aspartame for use in dry foods and as a table-top sweetener. Two years later Mark Novich, as acting commissioner, approved aspartame for use in soft drinks. Soon after Dr. Hayes left the agency and took a job as senior medical consultant for Burson-Marsteller, a public relations agency that represents Searle. The company says Dr. Hayes, who is also dean of New York Medical College, has never consulted on anything having to do with aspartame or any other product he ruled on at the drug agency.

MANY FACTORS IN POPULARITY

Among the reasons aspartame is so popular are that it provides the sweetening power of sugar at one-tenth the caloric cost; unlike products made with saccharin, it does not carry a warning about cancer risk and it tastes very much like sugar but, unlike saccharin, has no unpleasant aftertaste.

The drug agency has set an allowable daily intake of 50 milligrams of aspartame per kilogram of body weight, and the agency predicted that actual average use would run around eight to ten milligrams. According to Dr. Gault of Searle, levels of use found in a national survey last spring showed that the average was then already twice that—19 milligrams—and the maximum level consumed by "aspartame abusers" was 28 milligrams. A United States attorney representing the F.D.A. said in court last month that average consumption is now 30 milligrams and that many consumers are above the 50 milligrams maximum suggested.

According to Dr. Wurtman, some consumers can easily reach consumption levels that have been linked in animal studies to adverse effects on brain chemicals. Ironically, he added, those using the sweetener to control calories may be defeating their purpose, since his studies show high levels of aspartame may trigger a craving for carbohydrates by depleting the brain of a chemical that registers carbohydrate satiety.

Dr. Conners is worried about aspartame's effects on certain highly sensitive individuals. He has studied two young children who suffer extreme agitation following doses of aspartame equivalent to the amount found in a six-ounce serving of Kool-Aid sweetened with NutraSweet. One of the children becomes so agitated he has to be restrained, Dr. Conners said. The other, who is sensitive to sugar, becomes even more aggressive when given aspartame, he said.

Aspartame is the product of two amino acids (the chemical building blocks of protein), aspartic acid and phenylalanine, which are found in rather large amounts in ordinary protein-rich foods. When digested and metabolized, aspartame breaks down into its component amino acids and methyl alcohol.

Scientific concern has focused on phenylalanine, since some people are unable to process it properly, causing a buildup in the body that can damage the developing brain. A phenylalanine buildup, should it occur in response to aspartame, could endanger an unborn child whose mother has high levels of phenylalanine in her blood in pregnancy, some scientists say. Dr. William Pardridge of the University of California at Los Angeles, for one, is worried about possible detrimental effects on I.Q. in the children of phenylalanine-intolerant women who consume large amounts of aspartame in pregnancy.

Phenylalanine is also the precursor to tyrosine, a neurotransmitter in the brain. A recent study in rats by researchers in Dr. Wurtman's laboratory showed that aspartame can cause large buildups of phenylalanine and tyrosine in the brain. However, Dr. Wurtman has noted that rats process phenylalanine differently from people. He added that a federally financed study of the behavioral effects of aspartame in animals and people was now under way in his laboratory.

[Western Union Telegram, Apr. 22, 1985]

Senator HOWARD METZENBAUM,
Capitol One DC.

With your permission I would like to amplify some of my responses to the questions that you asked me during the recent committee hearings on artificial sweeteners:

1. Many foods besides aspartame apparently cause chemical changes in the brain. Examples include virtually all carbohydrates (sugars and starches), proteins, lecithins, and caffeine. However, the particular changes that follow aspartame consumption have not been associated with other foods, and thus must be fully evaluated to determine their effects on health and behavior. This evaluation should be pursued vigorously. Hereafter it must be assumed that all new food additives will require a similar careful evaluation.

2. For the reasons that I indicated, I believe it is important that food labels should now include the quantities of aspartame that the products contain. I also believe, though, that similar information should be provided about their contents of other food additives, because this is good nutritional policy; because health questions have also been raised about other sweeteners; and because the biologic effects of combining two chemicals (like sweeteners) can sometimes be quite different from the effects of giving the individual compounds by themselves.

3. I am not proposing that the ADI for aspartame be changed at this time; I'd have difficulty justifying any specific number rigorously. Rather, I believe that the ADI should be subject to continuing review, as new information about aspartame's effects (or lack of effects) accumulates. Ultimately I would like to see labels also include information about the upper limits of daily consumption for children and adults, but for the present, I believe that indicating the quantities of aspartame in each product would constitute an important and necessary first step.

4. I believe that well designed, placebo-controlled clinical studies should be initiated, particularly on aspartame's possible involvement in headaches and in lowering seizure thresholds. These studies should also determine whether aspartame metabolism is abnormal in subjects who develop such side effects (for example, whether the plasma amino acid pattern changes abnormally after aspartame consumption). The proposed studies should use ADI doses of aspartame, given acutely and chronically for many days, in circumstances similar to those in which people may actually use the sweetener (for example, taken along with some dietary carbohydrates and by people on weight reduction diets). I hope soon to initiate such studies at MIT's clinical research center, and understand that other institutions are also doing so.

Thank you for considering these comments.

Sincerely yours,

RICHARD WURTMAN, M.D.,
Professor, M.I.T.

UNIVERSITY OF CALIFORNIA,
LOS ANGELES,
April 22, 1985.

Statement to Senator HOWARD METZENBAUM:

Thank you for giving me the opportunity to express my views on the potential safety issues related to the effects on the brain of high dose usage of a new dipeptide sweetener, aspartame.

1. If high dose aspartame usage does have harmful effects, the sequelae are likely mediated via the phenylalanine component of aspartame, and not via the two other components of the compound, e.g., aspartate or methanol, or via the dipeptide itself. Among the tissues of the body, the brain is selectively vulnerable to large increases in blood phenylalanine. Thus, if aspartame is to have any harmful effects, it is most likely that the brain will be the target organ of aspartame-induced sequelae. Indeed, the Center for Disease Control recently concluded, "the highest priority for any in-future investigation might be in the neurologic/behavioral area".

2. A central question is, "what is a substantial increase in blood phenylalanine caused by aspartame ingestion?" The 1980 Public Board of Inquiry concluded that a minimum toxic threshold of blood phenylalanine of 0.5–0.6 mM may be used in man, and blood concentrations below this critical threshold may be considered harmless. If the threshold concept is true, then I do not believe that aspartame will cause harmful effects since even high dose aspartame usage will rarely cause an increase of blood phenylalanine up to 0.5–0.6 mM. However, a review of the medical literature indicates that there is insufficient evidence to conclude that the relationship between high blood phenylalanine and brain disorders follows a threshold relationship. Recent evidence indicates that the relationship between blood phenylalanine increases and brain effects is a linear one (1,2), and that changes in brain function occur when blood phenylalanine rises in increments of 0.25 mM (1,2). For example, there is a 10.5 point drop in I.Q. in infants born of mothers with blood phenylalanine increases in the range

of 0.25 mM over normal levels (1,3). Another study shows that neuropsychologic performance in children, e.g., choice reaction time, is altered when plasma phenylalanine is increased in the 0.25 mM range (2). These two studies are illustrative in that they describe effects in the two groups who are most at risk to develop high blood phenylalanine: (a) developing fetuses, owing to the ability of the placental membrane to concentrate phenylalanine inside the fetus, and (b) 7-12 year old children who, owing to their reduced body weight, consume high doses of aspartame in terms of mg/kg/day.

3. The studies showing effects on the brain in man of blood phenylalanine in the 0.25 mM range are of importance since the available data indicates that plasma phenylalanine will increase to this level in humans consuming aspartame on the order of 25 mg/kg, three times a day, particularly in heterozygotes (4) (and there is an estimated 4-20 million heterozygotes in this country) (1). Although 25 mg/kg three times per day, or 75 mg/kg/day, is nearly ten-fold greater than the expected FDA or industry projections of aspartame intake, the evidence in the literature indicates this is a likely daily intake for many consumers. For example, 7-12 year old children are found to consume up to 77 mg/kg/day (5). Normal weight adults are found to consume up to 32 mg/kg/day (6).

On the basis of the likelihood of a linear relationship between blood phenylalanine increases and brain function, I think it is essential that a case be made for labeling products with the mg of aspartame per product on the label. Thus, the physician who attempts to relate any possible neurologic/behavioral effects to aspartame intake may be able, through dietary survey, to compute the patient's average daily intake of aspartame in mg/kg. For example, if the physician determines that the daily intake is 10-20 mg/kg, then it is very unlikely that the patient's neuologic/behavioral problems are related to aspartame. On the other hand, if the daily intake is on the order of 50-75 mg/kg/day, then the physician may undertake a retrospective and prospective analysis of the possible relationship between aspartame-induced high blood phenylalanine and the patient's neurologic/behavioral problems.

Yours very truly,

WILLIAM M. PARDRIDGE, M.D.,
Associate Professor of Medicine.

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SEVERE BEHAVIORAL REACTIONS TO ASPARTAME IN A FOUR YEAR OLD BOY

(C. Keith Conners, Karen Wells, Sandra Kronsberg and Ellen Schwab)

BACKGROUND

The subject of this study is Stephen, a 4 year old boy who was referred for evaluation by his mother. During August of 1983 mother had begun providing Stephen with Sugar Free Kool-Aid with NutraSweet (Cherry artificial flavor) over a period of 3 weeks. He was thought to drink approximately 20 ounces/day in a more diluted form than called for on package instructions.

His behavior became increasingly erratic over this period (as reconstructed by the mother later). He became tearful, easily frustrated, had unprovoked angry outbursts and was extremely irritable. This culminated in a dramatic episode in which he became inconsolably and wildly emotional. He had to be isolated to his room where he repeatedly ran full force into the wall, knocking himself to the floor, crying, and repeating the performance until he was restrained.

Mother called her pediatrician who suspected that the new Kool-Aid might be responsible, and advised her to remove it. She did so and his behavior then returned to normal within 24 hours. About 2 weeks later the mother re-introduced the Kool-Aid, whereupon another violent reaction occurred within about 30 minutes. This episode subsided the same day. Suspecting the Aspartame in the drink, mother called us upon the advice of the pediatrician who had heard of our interest in sugar products and behavior. After some hesitation, she agreed to examine the problem in an experimental, double-blind fashion. An informed consent was obtained.

HISTORY

Stephen weighed 10.5 pounds at birth. Mother gained 55 pounds during pregnancy (twice the recommended amount), and delivery was 2.5 weeks late. He was described as "a great baby, a good sleeper and good eater." He had some feeding problems as an infant, exhibiting rhinitis and diarrhea following feedings of formula. He eventually tolerated formula feedings of Similac with iron (a cow's milk formula). Upon examination he was found to be a well-developed, well-nourished four year old at the 30th percentile of weight (16 kg) for his stature (105.4 cm).

Stephen is reported to be a very active boy, "going all the time". He still naps every afternoon. He is described as quite oppositional, saying 'no' to everything. Mother appears to try to manage mostly by 'yelling and screaming', though she was observed to be quite tender and solicitous of Stephen in the waiting room. He is quite a happy boy on the whole, seems very bright and precocious, but he can be quite aggressive and "beats his brother (7 years old) to a pulp". Sugar appears to make him more energetic.

There is some question of a possible milk allergy and allergy to molds. Mother says she cannot eat apples, pears, peaches or plums because of allergy to pectin. She is also allergic to jellied candies, pollen, penicillin and macrodantin.

Stephen's mother filled out a 93-item parent questionnaire (Conners Parent Questionnaire). The Restless-Impulsive factor showed an elevation of about 2 standard deviations, but was otherwise within normal range.

METHOD

Ratings. Mother was asked to fill out the 10-item Hyperactivity Scale on a daily basis. These items measure restless, impulsive, emotional behaviors. She was asked to obtain data over a 2-week period to establish Stephen's baseline.

Observations. On four occasions, about one week apart, Stephen and his mother returned to the hospital where they were observed through a one-way mirror for an hour or more. For the first half of the session mother was instructed to simply sit in the room and let Stephen do whatever he wanted. A variety of toys were available and he was asked to play by himself while mother sat and busied herself with some work. For the second half of the hour mother was instructed to issue various commands, such as "pick up the toys", "clean up the room", "sit in the chair", etc.

The behavior was videotaped from the other side of the room and later scored blind (without knowledge of the conditions) by an experienced behavioral observer. Behavior was coded in 15-sec blocks using an interval-sampling procedure developed by Hanf and Forehand. The main category of interest is child noncompliance to commands. Other categories include "whine/cry", and "destructive".

Challenge. Just prior to each observation period Stephen was given a 6 ounce cup of Cherry Kool-Aid to drink. On two occasions this was the sugar-sweetened version and on two occasions it was the NutriSweet version. The dietician (E.S.) made the determination of order of challenge, and neither parent, child, nor other observers had knowledge of the sequence. As it turned out, the sequence chosen was ABAB, with A=Aspartame, B=Sugar.

RESULTS

The results of the Hyperactivity Ratings is shown in Figure 1. After a stable baseline there is a clear increase in deviant behavior on the Aspartame days compared with the sugar days.

Figure 2 shows the percent of scoring intervals during which noncompliance occurred. Again there is a substantial increase in this behavior during the Aspartame challenge days.

Followup. Mother has continued to restrict Stephen from Aspartame, but on several occasions he has accidentally had drinks provided at school or at friends' parties. On each and every occasion mother claims that he has become quite disturbed. On one of these occasions he became very tearful and repeatedly said something was wrong, crying "Mommy, Mommy, please help me, I can't stand it."

Conclusion. We cannot be sure at this point that the observed reactions were truly due to the Aspartame. The artificial color in the drink is another possibility. It is also possible in a child that has a high rate of deviant behavior, that occasional challenges could, by chance coincide with an episode. One cannot, of course, generalize beyond this single case.

However, we are inclined to believe that the clear results from both direct observation and home observations, obtained under strict double-blind conditions, are sufficiently compelling to conclude that Aspartame (and/or its vehicle) are causing deviant behavior of quite severe proportions in this boy. We believe that further study of this problem in children is clearly indicated.

[From the Am J Psychiatry 142:2, February 1985]

INTERACTION OF ASPARTAME AND CARBOHYDRATES IN AN EATING-DISORDERED PATIENT

SIR: Wurtman (1) has pointed out that the acute ingestion of aspartame, particularly when combined with carbohydrates, can have a marked effect on the level of tyrosine in the brain. He speculated that the re-

sulting acute elevation of brain tyrosine level might induce behavioral or functional changes in the predisposed individual. In the following clinical case this appears to have happened.

Ms. A, a 22-year-old white woman, began to binge eat and purge soon after she developed secondary sexual characteristics at age 13. This habit evolved into a binge-purge cycle that took place an average of 15 times a day; she had a marked fear of obesity and a craving for carbohydrates. At age 21 she was placed on a regimen of fenfluramine and metoclopramide for her bulimia. Within a few weeks she stopped binge eating and vomiting. She then began to restrict her food intake excessively; her weight began to decrease and she became increasingly depressed. When her weight reached 79 lb, she was hospitalized. In addition to behavioral and psychotherapeutic treatments, she was given full therapeutic trials of imipramine, desipramine, and nortriptyline for her depression, which persisted despite her regaining a normal body weight. As an outpatient, she developed the habit of chewing her food and spitting it out to enjoy the sweet taste of carbohydrates and to avoid the excess calories. Each day she used about 10 packets of an artificial sweetener that contains aspartame. She was given a trial of a monoamine oxidase inhibitor (MAOI) to treat her "tricyclic-resistant" depression.

After being on a regimen of 10 mg/day of tranylcypromine for approximately 2 weeks, the patient noticed severe headaches that coincided with times when she was eating and spitting out high-carbohydrate foods and consuming the aspartame. She described the headaches as throbbing and said she felt flushed and sweaty. On each of five occasions when she experienced these symptoms, the headaches stopped within a few hours of stopping ingestion of the sweetener.

Ms. A refused to take the artificial sweetener and have her blood pressure checked. The headache was sufficiently unpleasant and the correlation between the ingestion of the sweetener and the headache was so strong that she preferred to use saccharine, which did not produce further headaches.

In this clinical case it appears that aspartame combined with carbohydrates led to the symptoms one might expect from an elevated CNS level of tyrosine in a patient who was taking an MAOI. It is important to keep this possible interaction in mind, particularly with the increased use of MAOIs to treat patients with eating disorders and atypical depressive states.

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(From the Annals of Internal Medicine, Vol. 102, No. 2, February 1985)

ASPARTAME-INDUCED GRANULOMATOUS PANNICULITIS

(By Nelson Lee Norick, M.D.)

The low-calorie artificial sweetener, aspartame (NutraSweet; G.D. Searle & Co., Skokie, Illinois), a synthetic combination of aspartic acid and the methyl ester of phenylalanine, is currently used in many diet sodas, cereals, and chewing gums and as a substitute for granulated sugar. Although the Food and Drug Administration has approved aspartame for routine use (except in patients with phenylkentonuria), its potential for toxicity remains controversial (1-4). This report describes the first confirmed case of aspartame-induced granulomatous panniculitis.

A 22-year-old, otherwise healthy woman had numerous, bilateral, nontender, nodular lesions on both legs for 2 months. The patient denied having used any oral, systemic, or topical medications during the preceding 6 months. She also denied any history of recent infections or trauma, and she had no accompanying constitutional symptoms. For the previous 6 years, the patient had habitually consumed between 1080 and 1320 mL (36 to 44 fl. oz) daily of a popular saccharin-containing diet soft drink. Approximately 10 weeks before presenting for evaluation, she had switched to the same manufacturer's new aspartame-sweetened diet soda. She made no other changes in her diet. Two weeks later, the patient first noted the onset of several nontender, deep nodules on her left thigh. New lesions subsequently appeared elsewhere on her legs while the previous lesions slowly enlarged; none disappeared.

On examination, numerous deep nodules ranging from approximately 0.5 to 5 cm in diameter were palpated bilaterally on the thighs and calves. The overlying skin appeared normal. The nodules were firm and in some areas coalesced to form large deep plaques that were freely movable over the underlying facial tissues. No adenopathy or other cutaneous or mucous membrane lesions were present; the rest of the general physical findings were normal.

Complete blood and differential count, erythrocyte sedimentation rate, serum electrolyte and amylase levels, and urinalysis findings were normal; liver function tests, serum protein electrophoresis, direct and indirect immunofluorescence studies, tuberculin tine test, and tests for antinuclear antibody and anti-steptolysin-O were negative. The patient refused a chest roentgenogram. Histologically, a septal panniculitis with lymphocytes and histiocytes predominated within the thickened fibrotic septae. Many multinucleated histiocytic giant cells and a lymphohistiocytic infiltrate extended into the adjacent fatty lobules, consistent with erythema nodosum.

The patient was advised to stop using the recently introduced aspartame-sweetened beverage. During the next 4 weeks, no new lesions appeared and all previous lesions spontaneously resolved without residua. She was then advised to resume daily consumption of the suspected aspartame-sweetened diet drink; 10 days later, she again developed the nodular lesions on both legs, this time in greater number that before. Withdrawal of the beverage once again resulted in gradual and complete resolution of all lesions.

The patient was next challenged with pure aspartame, 50 mg four times daily, in capsule form (supplied by G.D. Searle & Co.). Ten days later, nodules reappeared on her legs. Withdrawal of aspartame resulted in spontaneous clearing of all lesions.

Widely used, aspartame is 180 times sweeter than sucrose and is metabolized primarily to aspartic acid, phenylalanine, and methanol (5). No previous reports could be found in the literature conclusively linking aspartame to any cutaneous eruptions. (6). Several unconfirmed reports of "dermal eruptions" and urticaria have been received by the manufacturer according to Robert L. Alberti, M.D., Director of Medical Communications, G.D. Searle & Co. In addition, the Adverse Drug Reaction Report System of the American Academy of Dermatology has received on unconfirmed report of a macular, erythematous, confluent pruritic eruption in a man who had consumed large amounts of an aspartame-sweetened diet cola (Report no. 1170031284, reported 12 March 1984 and transferred to the FDA 10 April 1984).

The precise classification and pathogenetic mechanism of the panniculitis in my patient are unclear. Absence of tenderness in lesions, overlying skin changes, constitutional symptoms, and residual pigmentary changes upon resolution is inconsistent with erythema nodosum (7), whereas the histopathologic finding of septal panniculitis strongly favors that diagnosis (8).

The formation of toxic metabolites of aspartame, either during the drugs shelflife or as metabolic byproducts, offers one possible explanation for the reaction seen in this patient. Boehm and Bada (9) have recently reported that the heating of aspartame results in conversion of some of its amino acids to their racemates. Although they note that the possible toxicity of consuming large amounts of these racemates remains to be determined, they speculate that some food or beverage components may catalyze the racemization of aspartic acid and phenylalanine in aspartame at room temperature. Furthermore, despite extensive prior testing, no such reaction has yet been reported, suggesting that this phenomenon may be idiosyncratic rather than dose-related. Fortunately, in the present patient, mere discontinuation of the aspartame-containing beverage resulted in complete and relatively rapid resolution of the condition without residua.

(From the Food Chemical News, Apr. 15, 1985)

INTERNAL FDA UNCERTAINTIES ABOUT ASPARTAME SAFETY REFLECTED IN 1981 MEMO

A 1981 briefing memorandum on aspartame reflects internal Food and Drug Administration uncertainties about the safety of the artificial sweetener in the months immediately preceding the decision of then FDA Commissioner Arthur Hull Hayes to permit its use as a food additive.

The May 19, 1981 briefing memorandum which was referred to during recent hearings on the extension of the saccharin moratorium (See FOOD CHEMICAL NEWS, April 8, Page 26), reveals that statisticians in FDA were uneasy about concluding that the brain tumors observed were not statistically significant and that questions were also raided about the conduct of the studies.

"I do not concur that aspartame has been shown to be safe with respect to the induction of brain tumors," Robert J. Condon, of FDA's Center for Veterinary Medicine, wrote in a "dissenting opinion on the brain tumor issue," explaining that his opinion was "based on. . . three reasons: (1) positive results seen. . . for female rats (in one of the studies); (2) problems in the conduct (of two of the studies); and (3) power of the studies."

Similarly, a memo from Satya D. Dubey of FDA's Center for Drugs and Biologics, pointed out "certain statistical difficulties" associated with the key studies "within the framework of statistical principle, theory, method and practice."

The two statisticians were members of the Commissioner's Team on Aspartame, as was Douglas L. Park, now with the Center for Food Safety and Applied Nutrition, who noted in a memo that "the available evidence is limited and provides clear proof neither of the safety nor of lack of safety."

Appendices to the memorandum made available following the hearing reveal that FDA scientists also questioned the data on risk of aspartame ingestion in terms of amino acid imbalance, a question raised also by outside researchers, specifically MIT's Dr. Richard Wurtman.

One of these appendices cautioned that "a four-fold increase in phenylalanine might cause some adverse effects if the diet is deficient in protein."

Another, prepared by FDA's Barry N. Rosloff, of the Center for Drugs and Biologics, pointed out that conclusions on aspartame were dependent "on how well the studies performed reflect the conditions of anticipated usage, particularly regarding (1) dose levels, (2) concentration of aspartame in solution, and (3) concomitant consumption of food, particularly carbohydrates."

"The latter factor is particularly important since the presence of carbohydrates has been shown to reduce the increase in plasma glu (glutamic acid) seen with MSG feeding," Rosloff noted.

Noting the studies with aspartame were performed with orange juice or a flavored beverage base and there there was no information on how much carbohydrate was present in the vehicles or when food had last been consumed by the subjects, Rosloff commented, "Hopefully these variables do not deviate in a significant way from the anticipated conditions of aspartame consumption."

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HOW SAFE IS YOUR DIET SOFT DRINK?

(By Florence Graves)

(NutraSweet has been touted as the most tested food additive in history, but our investigation reveals such serious flaws in the government's approval of NutraSweet that Congress should begin its own investigation immediately.)

NutraSweet, America's newest sugar substitute, has been an overnight sensation. Low in calories, with a taste almost like sugar, NutraSweet is not only converting former saccharin users but drawing consumers away from sugar as well. Robert Shapiro, president of the NutraSweet Group at G.D. Searle & Co., which owns the patent on NutraSweet, declared at a gathering of soft drink companies last December that NutraSweet is "one of the most important developments in the history of food and beverages." In a recent interview with Common Cause Magazine, Shapiro said he realizes that NutraSweet "sounds too good to be true."

Ironically, Shapiro may be right. A Common Cause Magazine investigation based on dozens of interviews and a review of thousands of pages of documents, many obtained under the Freedom of Information Act, raises serious concerns about whether the Food and Drug Administration (FDA) established that aspartame—the scientific name for NutraSweet—is safe. The investigation shows that some scientists say tests have not resolved major health issues—including whether aspartame can cause cancerous brain tumors, and whether it can affect brain chemistry and therefore behavior. The magazine has also learned that some scientists have serious concerns about the sweetener's potential effects on children and pregnant women.

Meanwhile, the FDA acknowledges receiving at least 600 consumer complaints relating to aspartame. In these complaints—which Common Cause Magazine obtained under the Freedom of Information Act—people allege that they have suffered headaches, rashes, dizziness, menstrual problems and seizures after consuming aspartame. The complaints, most of which were received this year, are being investigated by the Centers for Disease Control in Atlanta.

Our investigation reveals such serious flaws in the FDA's approval process that Congress should begin its own investigation immediately. The investigation shows that then FDA commissioner Arthur Hull Hayes approved aspartame three months after taking office in April 1981, despite the fact that some of the FDA's own scientists had serious reservations about the validity and quality of pivotal tests used in his decision. (Hayes, through an assistant, refused to be interviewed.)

Hayes' decisions to approve aspartame for use in dry foods such as cereals in 1981 and soft drinks in 1983 does not square with the role the FDA is supposed to play. The FDA is the government agency that reviews and approves all tests submitted by companies before allowing food additives on the market. The law requires a manufacturer—in this case, Searle—to prove to the satisfaction of the FDA that there is a "reasonable certainty" that a food additive is safe. The government does not have to prove that it is harmful—an important distinction. If tests are inconclusive, an additive is not supposed to be approved by the FDA.

In deciding to allow aspartame in dry foods in 1981, Hayes ignored not only the recommendations of some FDA scientists, but also a recommendation by a 1980 scientific Public Board of Inquiry appointed by the FDA. The board said aspartame should not be approved because it had not been conclusively shown that the sweetener did not cause cancerous brain tumors. The board called for further testing to resolve the issue. In 1983, just two months before leaving office, Hayes approved aspartame for use in soft drinks, dramatically expanding its use.

Hayes defended his 1981 approval, saying, "Few compounds have withstood such detailed testing and repeated close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety."

But in fact, a 1975 special FDA task force had raised serious concerns about a number of the tests that Hayes eventually relied on in his decision to approve aspartame. Despite the fact that one former FDA commissioner said what was discovered about a number of Searle's tests—including pivotal brain tumor tests—was "reprehensible," our investigation shows serious questions about the tests were never resolved and the tests eventually relied on were never repeated.

Consumer attorney James Turner, who has gone to court to try to force a public hearing on aspartame, charges that Hayes picked "his way through a mass of scientific mismanagement, improper procedures, wrong conclusions and general scientific inexactness." Turner represents the Community Nutrition Institute, a Washington, D.C.-based public interest group.

Two FDA officials have told Common Cause Magazine that Hayes was determined to push aspartame forward, in part as a signal that the Reagan administration was ushering in a new regulatory era. One official privy to some of the deliberations made at Hayes' level says the "people at the top" were not receptive to important concerns raised about the quality and validity of some of the key tests submitted in support of aspartame.

"There were real questions" about the reliability and interpretation of the data "that were glossed over" at the commissioner's level, this official says, adding that Hayes and his close associates wanted FDA scientists to concentrate on providing rationales for overturning the 1980 Public Board of Inquiry instead of focusing on the fact that there were unresolved issues about a number of key tests.

The financial consequences of Hayes' decisions are enormous for G.D. Searle & Co. A Kidder Peabody financial analyst says Searle's U.S. sales of NutraSweet and Equal (the powdered sugar substitute) reached $74 million in 1982. By the end of 1983, following soft drink approval in the summer, sales had jumped to $336 million. Most of that increase was accounted for by soft drink use, the analyst says.

Meanwhile, a number of scientists continue to raise questions about aspartame's safety, especially with the widely expanded soft drink market.

Dr. Walle Nauta, head of the 1980 Public Board of Inquiry and an institute porofessor in the Department of Psychology and Brain Science at the Massachusetts Institute of Technology (MIT), says "extensive testing" is needed regarding a theory raised by MIT's Dr. Richard Wurtman that consuming large amounts of aspartame—especially with carbohydrates—may affect brain chemistry. In light of the consumer complaints, Nauta said in a recent interview, "I would think [the FDA] should be following [the issue] with great concern. Dr. Wurtman may be right." Aspartame "may be harmful in the long run."

In extending aspartame approval to soft drinks, Hayes dismissed Wurtman's concerns, saying his hypothesis is not supported by his data. The FDA says it is not requiring tests concerning Wurtman's theory.

Searle's Robert Shapiro agrees with the FDA, and Searle has said that "the various hypotheses suggesting a potential health risk from aspartame consumption are not supported by the scientific evidence submitted by Searle and exhaustively reviewed by FDA prior to aspartame's approval."

In an interview, Sanford Miller, chief of FDA's food safety division, defended the FDA's approval and said, "The same dead horses keep getting dragged up again and again and again."

Miller said aspartame is the most tested food additive in history, and he points to the more than 100 tests Searle submitted to the FDA.

But as one FDA scientist said in an interview, it doesn't matter how many tests are done on a food additive, the proper question is, how many of them are valid? And do they prove the additive is safe?

The key element of the controversy is that the vast majority of the tests—90 of 113 entries—were submitted by Searle in the early to mid-1970s. All aspartame tests submitted during that period by Searle and its major contractor, Hazleton Laboratories Corp., were called into question by a 1975 FDA special task force investigation. The special task force's findings were so serious that they led the FDA general counsel to request a grand jury investigation of Searle.

All aspartame tests that have been described by the FDA as "pivotal" were conducted during this period. Eighty-eight percent were done by Searle or Hazleton. Dr. Alexander Schmidt, FDA commissioner from 1972 to 1976, said in a recent interview that Searle's testing then was "incredibly sloppy science." He added, "What was discovered was reprehensible."

Schmidt says a pivotal test is one that is so important that it must be repeated if found invalid. The important question, he says, is, "Were there new pivotal experiments?" Our investigation shows that only one pivotal test was repeated. The FDA later said it was not used in the agency's safety assessment.

Despite the fundamental questions concerning the tests submitted before the end of 1975, Hayes and the Bureau of Foods relied on some or all of these tests when they made their decisions that aspartame is safe. Our investigation found no evidence in the public record that Hayes or the bureau

ever successfully explained how their decisions were reconciled with the questions raised by the special task force about Searle's flawed tests.

OTHER HIGHLIGHTS OF THE INVESTIGATION

Internal FDA documents obtained by Common Cause Magazine show that a number of significant deficiencies in the three pivotal tests used to determine whether aspartame might cause cancerous brain tumors were brought by FDA scientists to the attention of those advising Hayes during his deliberations, yet he decided to approve aspartame anyway.

A draft memo to Hayes on the brain tumor issue reads, "As you know, this is a subject upon which competent, neutral scientists have differed. The [FDA] Bureau of Foods found aspartame approvable on this ground. The Public Board of Inquiry found it not approvable without further testing. Your final decision, therefore, will largely reflect a policy judgment on how certain you want to be.". According to the law, if tests are inconclusive, an additive is not supposed to be approved by the FDA.

In reference to one of the pivotal brain tumor tests used to determine that aspartame is safe, Jerome Bressler, team leader of a 1977 special FDA task force investigating the test, told Common Cause Magazine that "you don't have to be brilliant to know . . . it was a lousy study; it was a sloppy study."

The Bressler team found evidence—including a photograph—that the experimental rats may not have eaten the intended doses of the test substance diketopiperazine (DKP), a breakdown product of aspartame. Bressler also recalls that there were indications that the rats found the DKP distasteful and may have avoided eating it.

Searle submitted 13 tests to try to establish that aspartame would not cause genetic damage. Memos in the public record show that the FDA scientists who initially reviewed the tests found serious deficiencies in all of them, describing three as "incomplete individually and collectively." Nevertheless, 1980 Public Board of Inquiry documents showed that although FDA officials acknowledged numerous problems with the tests, they decided that all the tests were good enough to rely upon in establishing the safety of aspartame.

Common Cause Magazine asked Dr. Marvin Legator, professor and director of environmental toxicology at the University of Texas medical branch in Galveston to review the FDA's reviews of the tests Searle submitted. Legator helped pioneer mutagenicity testing at the FDA, where he worked from 1962 to 1972. Although Legator says he has "no reasons to suspect that aspartame would be active," he says all the tests are "scientifically irresponsible" and "disgraceful."

"I'm just shocked that that kind of sloppy [work] would even be sent to FDA," and that FDA administrators accepted it, he says. Legator adds that "there is no reason why these tests couldn't have been carried out correctly. It's not that we are talking about some great scientific breakthrough in methodology."

In documents submitted to the 1980 Public Board of Inquiry, Searle said the tests were "adequate screening tests for mutagenicity." FDA would not comment on the tests because of pending litigation to get a public hearing regarding aspartame's approval.

In 1973 the FDA's Bureau of Foods asked the Bureau of Drugs to evaluate 10 tests on humans (called "clinical tests") submitted by Searle to determine "whether safety problems might be anticipated should this sweetener be marketed for general use." Memos found in the public record show that Dr. Martha Freeman, then of the FDA's Bureau of Drugs, concluded that "the information provided is inadequate to permit an evaluation of potential toxicity of aspartame."

Although the FDA does not require clinical testing for proposed food additives, Freeman recommended that "marketing for use as a sweetening agent should be contingent upon satisfactory demonstration of clinical safety of the compound," which she said would require more rigorous testing.

In an interview, Freeman said she made the recommendation because aspartame was an unknown substance whose toxicity was not known. "In general I think [unknown substances] should be more closely monitored than is currently done for food substances."

The Bureau of Foods rejected her recommendations and has continued to cite these 10 studies along with others conducted later as evidence of safety in humans.

The FDA opposed letting two critics—consumer attorney Turner and Dr. John Olney, professor of neuropathology and psychiatry at Washington School of Medicine in St. Louis—raise questions about the quality and validity of some of Searle's tests when the 1980 Public Board of Inquiry was convened.

The two critics had challenged the 1974 approval of aspartame, saying they believed that the sweetner might cause brain damage. They also questioned the validity of some key tests. In a 1977 letter to Turner, the FDA general counsel said that if Turner disagreed with the FDA's conclusions about the reliability of Searle's tests, "The Public Board of Inquiry on aspartame should provide a vehicle for a definitive resolution, at least for those studies about which you are most concerned."

Yet once the board was convened, the FDA argued that the board was not the proper forum for Turner and Olney to use to bring up their questions about the quality and validity of Searle's tests. The board agreed.

MIT's Dr. Walle Nauta, head of the 1980 scientific Public Board of Inquiry appointed by the FDA to review safety concerns about aspartame, said in an interview that scientists serving on the board had "concern about the validity of a number of the [test] data" supplied by Searle and challenged by Olney and Turner. But he continued with the board inquiry because "we had absolutely no way of knowing who was right"—the Bureau of Foods or Turner and Olney. "It was a shocking story we were told," he said, referring to the history of Searle's testing, but the board had "to take the FDA's word" that the tests in question has been properly conducted.

Nauta also said in an interview that the 1980 scientific review of aspartame "specifically excluded use in soft drinks." Soft drink use, he says, "never figured in our decision making."

Nauta also said he was surprised when the FDA approved aspartame for soft drinks three years later. He says FDA officials had told him that because aspartame breaks down in solution and when exposed to heat and loses its sweetness, its use in soft drinks would be "uneconomical." Nauta said the board "definitely" would have considered other tests and factors if he had known there were plans to eventually use the sweetener in soft drinks.

According to a draft objection obtained by Common Cause Magazine, within two weeks before aspartame was finally approved for soft drink use, the national Soft Drink Association (NSDA) appeared to have had enough concerns about the safe use of aspartame in soft drinks that it considered formally submitting an objection to the approval. NSDA science director Dr. Robert McQuate says the association didn't file the objection because all safety concerns were totally resolved. But a lengthy interview with McQuate leaves a number of troubling questions.

Searle and the FDA frequently point to the fact that aspartame has been approved in more than 30 countries and by the World Health Organization as evidence it is safe; Robert Shapiro, head of Searle's NutraSweet division, confirmed that approval in these foreign countries was based "essentially" on the controversial tests also submitted to the FDA. A financial analyst with Kidder Peabody of New York estimates that including U.S. sales, Searle will sell about $600 million of aspartame world wide in 1984.

Aspartame was discovered 19 years ago, when a scientist who was working on an ulcer drug absentmindedly licked his fingers and discovered a sweet taste. When aspartame was first approved in July 1974 for use in dry foods, such as cereal and powdered drinks, saccharin was the only low-calorie sweetener on the market. There were concerns that saccharin might cause cancer, and the serendipitous discovery of aspartame seemed to be the answer to dieters' dreams: a low-calorie sweetener made from natural products.

Aspartame, which is 180 to 220 times sweeter than sugar, is composed of two amino acids—phenylalanine and asparatic acid. But it really is a synthetic compound, because it is produced by isolating and synthesizing these two amino acids from the 20 or so usually found in a complete protein. Complete proteins are large, and take considerable time to digest. Aspartame, however, is a small molecule, and is digested quickly. Therefore, phenylalanine and aspartic acid are released quickly into the bloodstream.

It was up to Searle, as federal law requires, to establish a "reasonable certainty" that it was safe to consume this synthetic compound.

The company laid out its strategy for getting aspartame approved by the FDA in a December 1970 memo. The goal: "Bring [FDA officials] into a subconscious spirit of participation" with Searle.

The FDA said "yes" in 1974, but before aspartame could go on the market, consumer attorney Turner and Washington University scientist Olney formally objected, saying they believed that aspartame might cause brain damage. A former Nader's Raider, Turner has spent a great deal of his own money and the past 10 years fighting the approval. Both Turner and Olney were particularly worried about aspartame's potential effects on children.

Olney also believes that when aspartame-sweetened foods or drinks are consumed with foods containing monosodium glutamate (MSG), a seasoning used to enhance flavors in some processed foods and Chinese food, the chances of brain damage, particularly in children, are greater.

The FDA agreed in 1974 to hold a Public Board of Inquiry composed of scientists to consider Turner's and Olney's objections. But before the board could be convened, an FDA scientist stumbled across an irregularity in a test submitted by Searle on a drug called Flagyl, which is used to treat trichomoniasis, a sexually transmitted disease. This set off a controversy about the quality and validity of tests submitted by Searle on several drugs as well as the food additive aspartame.

The FDA's Dr. Adrian Gross, who is now with the U.S. Environmental Protection

Agency, recalled at Senate hearings in 1975 that when he first noted the discrepancies in the Flagyl test, none were "in any way 'alarming' at that particular point in time; they could have been nothing more than typographical errors. . . . We had no reason to suspect anything more serious than a simple error or mistake at that time."

But it took Searle two years to respond to questions about the discrepancies in the Flagyl test, Gross told the hearing. When the company finally answered, Gross found their response only raised more questions about the company's testing in general.

This led to additional investigations, and finally in 1975, then FDA commissioner Alexander Schmidt took the unusual step of appointing a special task force to investigate about 25 key tests Searle had submitted on seven products, including the drugs Flagyl, Aldactone and Norpace, and aspartame. The task force looked at 11 tests on aspartame, more than on any other individual product.

The task force report, which concluded that there were very serious deficiencies in Searle's operations and testing practices between 1967 and 1975, still lies at the heart of the controversy over aspartame's testing.

Before the task force had completed its investigation in 1976, Searle had submitted the vast majority of the more than 100 tests it ultimately gave the FDA in an effort to get aspartame approved. These included all tests ever described as "pivotal" by the FDA. About half the pivotal tests were done at Searle; about one-third were done at Hazleton Laboratories. "Pivotal" tests include long-term (two-year) tests such as those done to determine whether aspartame might cause cancer. Former FDA commissioner Alexander Schmidt said in a recent interview that if a pivotal test is found to be unreliable, it must be repeated "Some studies are more important than others, and they have to be done impeccably," Schmidt said.

Critics such as Turner say—and indeed the public record shows—that when the FDA approved aspartame in 1981, the agency had not successfully explained how the serious problems with the tests done during this period—including some pivotal tests—were reconciled with its decision to rely on a number of these tests.

Lead investigator Philip Brodsky, described in the 1975 task force report as "one of the FDA's most experienced drug investigators," recalled in an interview that he had "never seen anything" as "bad" as Searle's testing. " I wouldn't want to rely" on those tests "for making a decision about the products," he said; there were "too many errors."

When the task force submitted its report in March 1976, it reached some very serious conclusions. The investigation brought into question all of Searle's testing between 1967 and 1975, former FDA commissioner Schmidt said in congressional hearings, including pivotal tests eventually used as the basis for the 1981 and 1983 approvals of aspartame. The task force's conclusions, which were endorsed by Schmidt in congressional hearings, included the following:

"At the heart of the 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 Co., we have no basis for such reliance now."

"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."

"We have noted that Searle has not submitted all the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product."

"Finally, we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed or inaccurately analyzed or reported."

"While a single discrepancy, error or inconsistency in any given study may not be significant in and of itself, the cumulative findings of problems within and across the studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies. We have attempted to analyze and characterize the problems and to determine why they are so pervasive in the studies we investigated."

Investigators who looked at four chronic (i.e., long-term exposure) toxicity studies and one acute (short-term exposure) toxicity study found numerous discrepancies and problems with each of the five pivotal tests. They concluded that in all five studies, "the housing and control of animals was not adequate to insure the validity of the studies." According to documents submitted to the 1980 Public Board of Inquiry, the FDA Bureau of Foods used two of these as the basis for its conclusion that aspartame is safe.

Searle described the report of the 1975 task force as "incomplete, inaccurate in some instances" with "prematurely drawn and misleading conclusions."

At Senate hearings in 1976, Searle defended its testing, saying that it "believes that the scientific validity of the basic conclusions of its animal studies, and thus the safety of its products, has not been affected." The testing problems of Searle and others, however, led to the establishment of the FDA's Good Laboratory Practices regulations, which are now required industry-wide for tests that will be submitted to the FDA.

The FDA found errors and omissions so serious on several tests—including two aspartame tests—that in January 1977 FDA general counsel Richard Merrill wrote a 33-page letter requesting that the then Northern District of Illinois U.S. Attorney, Samuel K. Skinner, convene a grand jury. One of Merrill's charges: "Concealing material facts and making false statements in reports of animal studies conducted to establish the safety" of aspartame.

What happened to the probe? Dan Reidy, of the U.S. Attorney's office, says he can't discuss the issue at all because "once we use the grand jury investigation, we are bound by law to secrecy."

A Searle spokesperson says the grand jury investigation was dropped because there was "no validity to charges" of wrongdoing. Searle was "exonerated," the spokesperson said.

Task force lead investigator Philip Brodsky was surprised Searle officials weren't indicted. "I thought surely they would prosecute them," he told Common Cause Magazine. Former FDA commissioner Schmidt said in an interview that "my understanding was that the Justice Department didn't feel there was sufficient evidence of willful wrongdoing. It's hard to bring a criminal indictment on the basis of sloppiness."

Plagued by troubles, Searle, in the spring of 1977, hired Donald Rumsfeld, a former Member of Congress and secretary of defense in the Ford administration, as its president. He was brought in, a company official told one reporter, because Searle "wants someone with a Boy Scout image and Rumsfeld certainly has that."

For his part, Rumsfeld issued a statement saying he "was mindful of the challenges" that lay ahead. Within six months after Rumsfeld had taken over, industry analysts quoted in The Wall Street Journal said that Searle, whose fortunes had been failing, was "a 'likely turn-around candidate' this year because of the new chief executive's actions so far."

"Like any good politician," the article went on to say, "Don Rumsfeld keenly understands the importance of a public image. So, he has been mending fences with the FDA by personally asking top agency officials what Searle should do to straighten out its reputation."

In fact, "Our whole relationship with the FDA has improved," Westley M. Dixon, then Searle's vice chairman, told the Journal. He added that without Rumsfeld, "We wouldn't have gotten approval of Norpace," a drug that was also investigated by the 1975 FDA task force.

But approval for aspartame, a product that Shapiro says has been an unprecedented success for Searle, was still hanging in the balance. By the end of 1978, however, the picture began to brighten. The Journal reported that the Justice Department and a federal grand jury had dropped the investigation of Searle's animal testing.

The grand jury probe, triggered by findings in the 1975 investigation, was not intended to answer questions about whether all Searle's tests on aspartame were valid. The grand jury would only have determined whether there was enough evidence that Searle officials knowingly misrepresented findings to the FDA to prosecute those officials.

While the grand jury investigation was in progress, the FDA's Bureau of Foods still had to determine whether Searle's tests were valid. At this stage, the FDA had the option of requiring Searle to repeat, at a minimum, the pivotal tests. By repeating them, Searle could have presumably resolved the debate over the validity of aspartame's safety tests.

Instead, in 1977, the FDA decided to have another special task force look at three of Searle's pivotal tests. An internal FDA memo says this decision came after Searle and the FDA reached an impasse in negotiations concerning a proposal to have a group of pathologists from the Universities Associated for Research and Education in Pathology (UAREP) review a number of pivotal tests.

The results of this second special FDA investigation, known as the "Bressler Report" after team leader Jerome Bressler, revealed a number of problems with three pivotal aspartame tests.

For example, in one pivotal long-term rat study using DKP, an aspartame breakdown product, the scientists reviewing the Bressler Report found that "the question of whether the rats' diet was homogeneous cannot be conclusively resolved. Although there is no doubt that the animals ingested the DKP, it cannot be determined with certainty whether the intended doses were in fact ingested."

There were a number of reasons to question whether the feed had been properly mixed with the DKP. The FDA team found that "no homogeneity tests were performed on any batches of diet mix" used in the study. The team also found memos on two reports which said, "These samples were not homogeneous."

More evidence of concern: The Bressler Report also says that when FDA scientists were interviewing personnel about two

other tests, a former Searle employee, Raymond Schroeder, volunteered that "homogeneity may have been a problem in the DKP mixtures." In a follow-up phone call, the report says, Schroeder said he had seen the DKP mixtures and that "in his opinion, the particles of DKP were large enough to allow the rats to discriminate between the DKP" and the food.

But the third time the FDA interviewed Schroeder, "he seemed reluctant to make any positive statements," saying that after thinking about it, he was no longer sure about his previous statements to the investigators.

When contacted by Common Cause Magazine in May, Schroeder said he "hadn't really worked on" the test in question, nor did he recall volunteering information that the feed wasn't homogeneous. Relevant parts of the report were read to Schroeder to refresh his memory. Did the FDA scientists fabricate these conversations? "I'm not saying they're making it up," Schroeder replied, but "I don't recall being that emphatic."

Team leader Bressler told Common Cause Magazine recently that "you don't have to be brilliant to know" that "it was a lousy study; it was a sloppy study." Bressler also recalls there were indications that the rats may have found the DKP distasteful and therefore not eaten it.

Former FDA toxicologist Dr. Jacqueline Verrett, one of several scientists asked by the FDA to review the Bressler Report findings, also said in an interview, "There's no question about it, it was a lousy study." She agreed with Bressler that the "question about the homogeneity of the (rats') diet was a serious one."

Some FDA officials were apparently so concerned by the findings that they recommended that the FDA ask UAREP, which eventually reviewed 12 pivotal tests, to look at this study along with two others the Bressler team had investigated and found problems with.

FDA officials refused, saying that although the suggestion had "merit," the UAREP review wasn't necessary, an internal FDA document shows.

The Bressler review marked the second time the long-term DKP pivotal study had gotten a hard look. The 1975 task force investigators also found a number of problems and discrepancies with this study. The task force concluded that in this test—as in several others—"the housing and control of animals was not adequate to insure the validity of the studies," that treatment mixtures were not tested to see whether they were homogeneous, and that there were discrepancies in the protocols.

In addition, the report of the 1975 task force also said investigators were stumped by this incident: Although one Searle scientist had submitted a written evaluation of a tissue mass supposedly found on one of the rats, a technician had reported that he couldn't find a mass in the bottle.

The investigators said they asked the pathologist whether the missing tissue mass might be in another bottle. According to the report, the pathologist said that at the time the animals were sacrificed, "you should have seen things when this study was run—there were five studies being run at one time—things were a mess!"

FDA officials and Searle defend the study, saying that although there may have been problems, the study was still valid. Both the FDA and Dr. Daniel Azarnoff, president of Searle's research and development division, say one of several indications that the rats ate the required amount of DKP is the fact that a statistically significant number of rats developed tumors in their wombs (called "uterine polyps").

FDA officials asked several outside scientists to determine whether the uterine polyps were precancerous. The scientists decided they were not; therefore, the FDA said, there was no cause for concern.

But Turner and Olney see it differently. They say the fact that the rats developed polyps—precancerous or not—is an indication that DKP may pose health concerns. "Are you going to tell the American public, 'Well, don't worry, it's not going to cause cancerous polyps, all it's going to do is cause benign polyps?'" Turner says.

Turner and Olney say the fact that the rats got uterine polyps at what could have been very low or uneven doses of DKP is even more cause for concern. They say it is not unreasonable to assume that the rats could develop cancerous polyps at higher doses.

Despite the problems found by the Bressler team with this DKP test and the two others reviewed, the FDA decided to proceed with its plan to have the group of university pathologists review 12 other pivotal studies rather than making Searle do the studies again. UAREP's mission was to examine lab notebooks, recalculate tables and look at Searle's interpretations of microscopic slides to determine whether the information corresponded to what was reported to the FDA.

Like the 1975 task force investigation, this review also lies at the heart of the current controversy over Searle's aspartame tests. And like the report of the 1975 task force, the UAREP report raised as many questions as it answered. Although the FDA has tried to use this review as evidence that the questionable studies are valid, our investigation shows that the UAREP review does not establish the Searle tests are valid.

In the words of commissioner Hayes in his 1981 decision, UAREP was to "make sure that the studies were actually conducted." The pathologists were specifically told that they were not to make a judgment about aspartame's safety or to look at the designs of the tests. Both Olney and former FDA commissioner Schmidt said in interviews that examining the design of a test—that is, ascertaining whether it actually does what it purports to do—is one of the key factors in determining whether a test is valid.

Why did the FDA choose to have pathologists conduct an investigation when even some FDA officials acknowledged at the time that UAREP had a limited task which would only partially shed light on the validity of Searle's testing? The answer is not clear.

Dr. Kenneth Endicott, director of UAREP, said in an interview that the FDA had "reasons to suspect" that Searle's tests "were not entirely honest." Because the FDA "had doubts about (Searle's) veracity," Endicott said, officials wanted UAREP "to determine whether the reports were accurate."

FDA scientist Dr. Adrian Gross, in a letter to an FDA official, said, "speaking as a pathologist," it seemed questionable that the group could do the kind of comprehensive investigation that was required. He pointed in particular to a variety of issues that needed to be investigated. He said some of these would involve closely questioning administrators and lab technicians about their practices. Since many important issues that should be investigated "have nothing to do with pathology," he said, only trained FDA investigators were qualified to do a comprehensive evaluation of the testing.

Consumer attorney Turner also raised concerns, saying he was "unnerved" by the UAREP plan. That was when FDA general counsel Richard Merrill wrote Turner saying that if he disagreed "with FDA's conclusions on these issues, the Public Board of Inquiry on aspartame should provide a vehicle for a definitive resolution, at least for those studies about which you are most concerned."

Meanwhile, an interview with Endicott indicates that Adrian Gross was right: the pathologists couldn't—and didn't—carry out a comprehensive review. UAREP determined that Searle had not lied about the test data, but UAREP didn't do a searching investigation of how the tests were conducted.

As former FDA commissioner Alexander Schmidt put it in a recent interview, UAREP looked at the slides to determine whether they had been misrepresented, but didn't look at the conduct of the experiments in depth. The 1975 task force investigation looked at the conduct of the experiments in depth, but did not look at the slides.

In an interview, Endicott agreed that UAREP's conclusions did not mean the tests were valid. Although UAREP did comment on issues such as protocols, food consumption and the handling of data, Endicott said, "there were lots of other opportunities for error"—errors that would not have been in the record UAREP reviewed. "We could only look at what was there—the tissues," he said. In fact the 1975 task force had looked at a number of these other areas and had found Searle's testing wanting.

What other aspects of testing are important to the validity of a test?

Are laboratory practices important?

"Oh yes," Endicott said. The UAREP report said it had no way of evaluating lab practices when the studies were conducted.

But the 1975 task force investigation had revealed such serious problems with lab practices at Searle and other companies in the late '60s and early '70s that the FDA was prompted to develop detailed regulations on good laboratory practices, which all laboratories submitted tests to the FDA must now follow. Searle indirectly seemed to acknowledge its problems by developing its own laboratory practices regulations and providing a draft for the FDA to use in developing its industry-wide standards.

Is the quality of the personnel important?

"Oh, yes, very important," Endicott said, especially the credentials of the "senior people." The UAREP report said the pathologists didn't have enough information to evaluate the quality of the personnel.

The 1975 task force, however, did raise concerns about the quality and training of personnel. Pointing out that studies in reproduction and teratology (fetal damage) are an "extremely important phase in safety evaluation," the report says that "the person (at Searle) responsible for most of the reproduction studies reviewed was apparently inexperienced in conducting studies of this nature and yet given full responsibility at Searle with a title of senior research assistant in teratology. His prior experience was one year's employment with the Illinois Wildlife Service, where his work involved (the) population dynamics of the cotton tail rabbit."

The report continued: "When asked by investigators during an interview what qualifications or training he had for conducting reproduction and teratology studies, he replied that shortly after his employment he went to a meeting of the Teratology Society, and Searle provided him with any books on the subject he wanted. This individual was also responsible for the training and supervision of a research assistant and two technicians." By the end of 1975, Searle had

submitted 18 studies relating to reproduction and teratology.

Is animal care important?

"Oh yes, very important? Endicott said. "The main thing to guard against is introducing an error into the results because of improper animal care."

UAREP said it couldn't possibly evaluate animal care facilities at the time the tests were done, but noted that since 1968, Searle facilities had been approved by the American Association of the Accreditation for Laboratory Animal Care.

However, the 1975 task force said that although it also had no way of evaluating animal care facilities at the time the tests were done, the investigators found "poor practices" at Searle in October 1975. For example, they found that an exterminator hired to spray the animal rooms with insecticides twice a month used a fogging machine for two or three minutes without removing the animals from the rooms. "Evidence indicates this practice has been in effect at least since 1970," the report said. The investigators could find no evidence that treatment mixtures used in the studies had been tested for pesticide content.

Does the diet deteriorate in storage? Is it important that the test substance be uniformly mixed in the animal feed?

"That's very important. You might vary the dose," Endicott said.

The 1975 task force reported that in studies conducted by Searle and its major contractor, Hazleton Laboratories Corp., "little concern was evidenced for the need of proper quality control of homogeneity, concentration or stability of the active ingredient-diet." The report said that because of inadequate practices at both Searle and Hazleton, "there is no (italics theirs) way in which it can be assured that animals received the intended dosages."

UAREP reinforced these points in its report. Noting that the stability (the extent to which it deteriorates in storage) of aspartame and DKP are "obviously important to any interpretation of the results of these studies," the university scientists reported that some records indicated that the stability of aspartame was "uncertain." Furthermore, "to UAREP's knowledge, no samples were analyzed for stability of (aspartame) or DKP, or uniformity of mixing." Hazleton Laboratories told UAREP that "Searle did not request such tests."

UAREP offered to carry out "an independent analysis on the mixing characteristic," the report says, but Searle "declined" the offer.

At this point, the FDA was left with the following issues:

The 1975 task force had looked at a number of the pivotal tests and raised questions about all of Searle's tests—including the vast majority of the aspartame tests—done between 1967 and 1975.

The Bressler team had reviewed three pivotal tests and found a number of problems with those tests.

The designs of the tests apparently had not been reviewed by the Bureau of Foods since the tests have been submitted for the 1974 approval. The 1975 task force said it found problems in the designs of some aspartame tests.

UAREP had verified that 12 pivotal tests had been conducted, and that few, if any, of the discrepancies that the pathologists found would have changed the statistical results of the test. UAREP says it was told by both Searle and FDA not to evaluate the designs so "any interpretation of results applies only to the experiments as designed." UAREP also did not take responsibility for a number of aspects important to the way the studies were conducted—including animal care, lab practices and homogeneity of feed. UAREP also said its conclusions "are not necessarily representative of other Searle studies."

The FDA's Bureau of Foods relied upon a number of tests called into question by the 1975 task force investigators which were not reviewed by either the Bressler team or UAREP, according to 1980 Public Board of Inquiry documents. That leaves questions about how the FDA determined they were valid.

How did the FDA take all these factors into account when it decided that the tests were good enough to rely upon?

Our investigation found no evidence on the public record that the FDA successfully reconciled these factors.

In his 1981 decision approving aspartame for dry foods, Hayes argued that because the 1975 task force investigation "only peripherally" involved aspartame, it was "superceded" (sic) by the UAREP review of the 12 pivotal tests and the Bressler review of three other tests. In an interview, Sanford Miller, chief of the FDA's food safety division, also made this argument. But Hayes and Miller appear to be wrong. The 1975 task force investigation looked at 25 tests involving several drugs and aspartame. The task force looked at 11 pivotal aspartame tests, so it seems safe to say that aspartame was not a "peripheral" part of the investigation.

And who checked the Searle tests to see whether their designs, which are crucial to an evaluation, actually measured what they purported to measure? FDA official Dr. Anthony Brunetti says the FDA didn't need to check the designs of the tests because they had already been checked when the tests were first submitted for the 1974 approval of aspartame.

But Turner and Olney point out that because the conduct of Searle's tests had been seriously questioned by the 1975 task force, there is no reason that the designs of Searle's tests checked in 1974 should be considered reliable.

Asked whether he knows how the report of the 1975 task force was taken into account, Dr. Daniel Azarnoff, president of Searle's research and development division, replied, "I guess that was done by the FDA."

It seems reasonable to assume that if the FDA did resolve these questions in a deliberative fashion, there would be some written record or report. Yet the FDA has never brought forward any document to answer the questions that have been raised in various forums over the years—including the courts.

Nevertheless, the FDA decided the studies could be relied on, and then submitted them for the Public Board of Inquiry's review.

The 1980 Public Board of Inquiry was held because the FDA is required to have substantive objections to the approval of a food additive or drug reviewed. Ordinarily, public hearings are conducted by administrative law judges, but Turner and Olney had agreed with the FDA's suggestion to try something new: have scientists act in the capacity of judges. All parties—Searle, the FDA, and Turner and Olney—had a say in choosing the three scientists who served on the board.

The questions before the Public Board of Inquiry included:

Could aspartame cause cancerous brain tumors?

Could aspartame—either alone or in combination with MSG—cause brain damage resulting in mental retardation, endocrine dysfunction or both?

Turner and Olney argued that aspartame had not been proven safe. They were particularly concerned that the sweetener could expose people—especially unborn children and infants—to a considerable risk of brain damage leading to either mental retardation or endocrine dysfunction or both. Searle and the FDA's Bureau of Foods argued that aspartame had been proven safe.

Although Turner and Olney participated in the 1980 Public Board of Inquiry, they were not allowed to present their concerns about the quality and validity of the tests, including the pivotal tests.

Even though the FDA general counsel had said in 1977 that this should be the appropriate forum in which to raise these questions, Dr. Walle Nauta, head of the board, refused to allow questions about how the tests were conducted.

Nauta said he believed the board's job was to interpret the results of tests. He said the board had to assume that the tests had been well-conducted. Although Turner and Olney maintained that there were still major questions about the validity of the tests, the FDA and Searle argued at the Public Board of Inquiry that UAREP's review had validated the tests.

In an appeal to the FDA commissioner following the report of the 1980 Public Board of Inquiry, Turner wrote, "The entire argument that since the studies are no longer considered fraudulent by FDA they are therefore scientifically valid is an example of a rhetorical shell game that, if successful, can only bring discredit and ridicule on the FDA."

Was Nauta concerned about the questions Turner and Olney raised about the testing? In an interview in April with Common Cause Magazine, Nauta acknowledged that he was. He said the "general tenor" among board members was "one of worry" about the validity of the test data. "There was considerable concern," he said. "It was a shocking story we were told," about the history of Searle's testing, but "there was no way we could go after it. We had absolutely no way of knowing who was right. We had to take the FDA's word." So Nauta allowed the scientific inquiry to continue, based on an assumption that the tests were valid.

Olney tried to tell the board that he believed there were serious, unresolved questions about some of the pivotal tests—especially three brain tumor tests later used by commissioner Hayes in his decision that aspartame is safe. Tipped off by an FDA employee, Olney had filed under the Freedom of Information Act for a copy of the Bressler Report, done by the special team of FDA investigators and scientists. The team had reviewed three pivotal tests in 1977, before UAREP began its study. The Bressler Report raised questions about whether the rats in one key test—a test supposedly helping to prove aspartame does not cause brain tumors—had been fed sufficient amounts of the test substance, DKP, a breakdown product of aspartame.

Olney was incredulous when he found out that the FDA had never made this report part of the record to be reviewed by the board. In trying to make his case that the quality of the tests should be reviewed, he told the board there are "a number of disturbing irregularities and research deficiencies revealed in the Bressler Report, but I shall focus on a single item, a Polaroid picture of a feed mixture in which the test compound was so poorly integrated into the feed that a chemistry technician at Searle had to re-grind the feed mixture herself every time it was brought to her for assay (measuring)." Both Searle and the FDA [illegible] the photograph is evidence the problem was discovered and corrected.

Olney also told the 1980 Board of Inquiry that there were—among other concerns—serious questions about two other studies done to determine whether aspartame might cause brain tumors. These studies were later used in commissioner Hayes' decision that aspartame is safe. The first test, Olney says, "revealed a very high incidence of brain tumors, all confined to animals who were fed aspartame." A second test, "known to have been conducted under conditions considered 'sloppy at best,' continued to reveal exceedingly high brain tumor rates, but with the incidence perfectly balanced between experimentals [rats that consumed aspartame] and the controls [rats that didn't eat aspartame]."

Olney said it is unusual for the strain of rat used in the experiments to develop spontaneous tumors (that is, to have tumors develop without being exposed to a test substance). That's why Olney was surprised to find that the control rats in the second group experienced a high number of brain tumors. He suggested that there was evidence in the UAREP report that the controls in the second test may have been accidently exposed to aspartame, thus invalidating the test.

"Because there is reasonable basis for suspecting that such mixups could have occurred in the Searle tumor studies," Olney said, "these studies should be repeated."

The Public Board of Inquiry agreed that the tests results were "bizarre," and recommended that another long-term test be conducted. But in his 1981 decision overruling the board, Hayes said he believed both the board and Olney were wrong about the incidence of spontaneous brain tumors in the strain of rats used. Olney said in a recent interview that Hayes' reasoning was "arbitrary" and "irresponsible."

Hayes also said Olney's theory that both groups of animals in the second test may have been fed aspartame was "speculation."

Our investigation also turned up questions about the second test, in which both control and experimental groups got high incidences of brain tumors.

A Dec. 8, 1975 task force memo obtained by Common Cause Magazine states that this lifetime toxicity study in rats was "the most pivotal" of the tests being investigated by the 1975 task force because "it was designed to show the no-effect level" of aspartame. According to the memo, Richard Ronk, deputy director of the FDA's food safety division, said that if we were not possible to "reconstruct the tables from the raw data on the key study," then the FDA "would recommend revocation of the [Searle] petition" that aspartame be approved.

When UAREP reviewed the study, its report said that it has been "difficult to reconstruct and document the progression of the changes of the experiment. . . . This task was complicated by the fact that written instuctions requested all earlier versions of protocols [research plans] be destroyed as they were updated."

When these comments were read to Ronk recently, he noted that UAREP said it was "difficult" not "impossible" to reconstruct the test. Asked how UAREP's difficulties were reconciled, Ronk said, "I'm not going to express an opinion" because questions about aspartame's approval are now in the courts.

Without considering questions raised by Turner and Olney about the validity of the tests, the Public Board of Inquiry reached a decision. The board determined that aspartame—either alone or in combination with MSG—wouldn't cause brain damage or neuroendocrine regulatory dysfunction. Both Turner and Olney disagreed with this finding. But the board decided that there were too many unresolved questions about brain turmors, and recommended that another long-term test be conducted before aspartame was approved.

Both the FDA Bureau of Foods and Searle disagreed with the board's findings on brain tumors and concluded that aspartame was safe and should be approved. The final decision was in the hands of the FDA commissioner. In the fall of 1980, Searle filed suit in federal court in Washington, demanding that the FDA commissioner, then Dr. Jere Goyan, speed up the final decision.

And on January 16, 1981, just days before Reagan's inauguration, Searle wrote Goyan, President Carter's FDA commissioner, asking him to make a decision on aspartame before leaving office. "The aspartame proceeding has dragged on for more than six years. Searle has on numerous occasions expressed its concern over the inordinate delay and has pointed out the substantial expenses and erosion of our patent protection associated with the delays." (In December 1982, Congress passed a law permitting Searle to extend its patent, which is now scheduled to expire in 1992.)

Goyan left office without deciding, and Arthur Hull Hayes took over as commissioner in April 1981. A group of FDA scientist had been assembled to review the aspartame data and to make recommendations. Two FDA officials have told *Common Cause Magazine* that Hayes made it clear from the beginning that he wanted to push aspartame forward, in part as a signal that the Reagan administration was ushering in a new era of regulatory reform. Hayes refused to be interviewed for this story.

Hayes adopted the Public Board of Inquiry's decision that aspartame wouldn't cause brain damage.

But the brain tumor issue was a different story. An FDA source says questions regarding the validity of some of the tests being relied upon, especially brain tumor tests, brought to the attention of those close to Hayes, but "the people at the top were not receptive."

Instead, a source says, the scientists advising Hayes were encouraged to concentrate on arguments that could be used to overturn the Public Board of Inquiry's recommendation that aspartame not be approved because the brain tumor issue had not been resolved.

Despite what one FDA official described as "very serious" questions about some of the key brain tumor tests discussed at the time, Hayes overruled the board in July 1981 and approved the use of aspartame in dry foods. Accepting the Searle tests as having been conducted properly, he said he disagreed with some of the board's analysis on the brain tumor issue and he believed the board had made some erroneous statistical assumptions that change the interpretation of some test results.

The board had recommended that another long-term study on brain tumors be conducted, and Hayes pointed to a test that had just been completed by an aspartame manufacturer in Japan. However, Hayes acknowledged in his 1981 decision that he had only a "preliminary report" of the test and that it had not been reviewed in depth by the FDA. "Taking the available information at face value," he wrote, "this [test] appears to be negative in terms of brain tumors." He described the test as "additional evidence" which did not serve "as a central basis for my decision."

But an FDA source said that in fact the Japanese study figured prominently in Hayes' decision-making process, even though he claimed it had not.

This source says FDA lawyers assigned to write Hayes' decision phrased Hayes' comments on the Japanese study very carefully. Legally, Hayes could not use this test as a basis for his decision because it had not been reviewed in detail by the board or the FDA. One FDA source says that even though Hayes could not say the Japanese study was a basis for his decision, he wanted to hold it out as satisfying the call by the Public Board of Inquiry for another long-term test.

It appears that the strategy has worked. When Common Cause Magazine asked two members of the Public Board of Inquiry why, as reported in the press, they had agreed with Hayes' decision to overrule them, they both initially answered it was because of the additional evidence—the Japanese study. In interviews, Dr. Walle Nauta and Dr. Vernon Young, both of MIT, seemed to be under the impression the Japanese study figured prominently in Hayes' formal decision to approve aspartame. When Nauta was told that Hayes wrote in his decision that the Japanese study was not the basis of his decision, Nauta replied, "That's news to me." Young said, "If that's the case, I've been somewhat misled."

Nauta, who was chosen by the FDA to serve on the board, then said the statistical errors "should have been enough" for Hayes to overrule the board. Young then said he nevertheless agreed with Hayes' decision because of the additional study and the powerful arguments made by Searle in response to the Public Board of Inquiry decision. Young, who had been recommended by Searle as one of the board members, said his views are based on the assumption the tests were conducted properly.

The third board member, Dr. Peter Lampert, professor and chairman of the Department of Pathology at the University of California, San Diego, was out of the country, but an assistant said Lampert did not agree with Hayes' decision. Lampert had been chosen to serve on the board by Turner and Olney.

Two years after Hayes approved aspartame for use in dry foods and two months before he left office, he approved aspartame for use in soft drinks, again citing some of the same controversial tests done before the end of 1975.

Nauta told Common Cause Magazine he was surprised. He said the Public Board of Inquiry's decision "specifically excluded use in soft drinks." He "definitely" would have wanted to look more closely at other tests and factors if he had known soft drink use was being anticipated. But he says that at the time of the 1980 Public Board of Inquiry, FDA officials led him to believe that soft drink use was unlikely because aspartame breaks down in solution and loses its sweetness when exposed to heat, so use in soft drinks would be "uneconomical."

Aspartame breaks down into chemicals such as DKP and methyl alcohol. The FDA says this poses no safety concerns. Turner and Olney and others disagree. (See page 32.)

Nauta also said questions raised by MIT's Dr. Richard Wurtman after the 1981 Public Board of Inquiry and prior to soft drink approval should not be dismissed without "extensive testing." Wurtman says his preliminary tests indicate that large amounts of aspartame, especially when consumed with carbohydrates, may affect brain chemistry and therefore behavior. Given consumer complaints, Nauta said, "Dr. Wurtman may be right:" aspartame "may be harmful in the long run."

Hayes and the FDA's Bureau of Foods disagreed, saying Wurtman's hypothesis is not supported by his data. The FDA is not requiring testing of Wurtman's hypothesis.

Given the questions surrounding the validity and interpretations of a number of key tests, did Hayes' decision to approve aspartame meet the legal test that a food additive is safe if there is "reasonable certainty of no harm?"

An internal FDA document says, "The statute is quite clear: The proponent of a food additive petition must prove safety. This is very important because it is quite possible that the data may fall in the 'grey area' where the food additive has not been shown conclusively to be either safe or harmful."

As a precedent, the document goes on to point out that in the case of another sweetener, cyclamates, former FDA commissioner Jere Goyan concluded that because "the data were 'suggestive' of a carcinogenic effect, though admittedly inconclusive," he could not approve cyclamates. "It is in this same 'grey' area that Dr. Olney, Mr. Turner and the Board [of Inquiry] believe aspartame falls into," the document pointed out.

Internal FDA documents reveal that some scientists advising Hayes raised serious questions that the tests did not establish a "reasonable certainty" that aspartame was proven safe.

But Hayes, as the record shows, decided that the Searle tests were good enough.

Soft Drink Use—A Continuing Controversy

When the FDA approved the use of aspartame in soft drinks last July, Dr. Walle Nauta was surprised.

An institute professor in the Department of Psychology and Brain Science at the Massachusetts Institute of Technology (MIT), Nauta had chaired a 1980 Public Board of Inquiry convened by the FDA to examine concerns that aspartame might cause brain damage or brain tumors. The board members agreed that brain damage wasn't a concern. But the board believed that it had not been established that aspartame wouldn't cause brain tumors, and therefore recommended that aspartame not be approved. The board was overruled by then FDA commissioner Arthur Hull Hayes.

In an interview in April with *Common Cause Magazine*, Nauta said the 1980 scientific review "specifically excluded use in soft drinks. We were told by the FDA that aspartame in solution has limited life. . . . We took the whole conversation to mean it was unlikely [to be considered as a sweetner] in bottles or cans."

If he had known there were plans to add aspartame to soft drinks, would Nauta have conducted the Public Board of Inquiry differently? "Definitely, yes," he said. "We certainly would have had to look at other things," such as "what happens in the breakdown process."

Nauta also said he is concerned with the issue raised by Dr. Richard Wurtman that large amounts of aspartame, especially when consumed with carbohydrates, may affect brain chemistry and therefore behavior. Wurtman is professor of neuroendocrine regulation at MIT. Nauta said Wurtman's theory, which was raised after the Public Board of Inquiry met, needs "extensive testing."

"I would think [the FDA] should be following [the issue] with great concern," Nauta said. "Dr. Wurtman may be right;" aspartame "may be harmful in the long run." The FDA has said Wurtman's hypothesis isn't supported by his data.

The FDA's approval of aspartame (marketed as NutraSweet) for use in soft drinks last summer dramatically expanded sales. The approval has been "incredibly important," says one industry analyst, who points to a jump in U.S. sales of aspartame from $74 million in 1982 to $336 million in 1983. He says much of the dramatic increase can be attributed to soft drink use.

In light of the expanded use of aspartame with the approval for its use in soft drinks, three major concerns have arisen. There is sharp scientific controversy concerning these issues, but critics charge that the FDA:

Failed to recognize the possibility that large amounts of aspartame, especially when consumed with carbohydrates, may affect brain chemistry and therefore behavior;

Significantly underestimated aspartame consumption levels;

Failed to adequately address questions of safety raised by aspartame's decomposition products, among them diketopiperazine (DKP) and methyl alcohol (methanaol). Aspartame decomposes to these and other chemicals after sitting in liquids, particularly acidic liquids, and when exposed to heat.

Will NutraSweet Affect Brain Chemistry?

Those who had raised questions include the National Soft Drink Association (NSDA), which wrote a letter to the FDA in June of last year. Common Cause Magazine has also learned that NSDA considered filing an objection to FDA's approval of aspartame use in soft drinks. A draft of the objections spells out in detail several of these safety concerns, in addition to others (see related story, page 30). An NSDA official says the objection wasn't filed because all the safety concerns were resolved in the minds of NSDA officials.

But NSDA does agree with several scientists and consumer groups who believe additional research should be done to answer questions raised by Wurtman.

Wurtman, who testified in favor of aspartame before the 1980 Public Board of Inquiry—and who says he occasionally sprinkles Equal on his strawberries—does not believe aspartame should be banned. But he's worried about the significanty increased consumption posed by approval in soft drinks. As he explained in a letter to the editor in The New England Journal of Medicine last August, his "pilot studies" suggest that an increase in aspartame's use—i.e., in soft drinks—may cause "neurochemical changes that could affect behavior." Moreover, he said he found that the combination of aspartame and carbohydrates, which are found in foods such as sandwiches and cookies, increases the "sweetener's effect on brain composition."

In a June 1983 letter to the FDA, Wurtman suggested that approval of aspartame for use in soft drinks be withheld pending further tests. He pointed out that Searle "has nothing to gain from receiving FDA approval now and then finding out six months from now that the aspartame-carbohydrate combination seriously alters brain neurotransmitters in rats, or behavior in humans."

With final FDA approval imminent, Wurtman wrote the FDA in August 1983, saying while he felt "moderate levels of aspartame in the diet are likely to be safe . . .," he would feel more comfortable if the FDA would place a limit on the amount of aspartame soft drinks could contain. While most soft drinks companies are using a combination of aspartame and saccharin, they are doing so primarily because aspartame is so expensive (about $90 a pound, to saccharin's less than $4 a pound) and because it decomposes after sitting in solution or at high temperatures. There's nothing to stop companies from using 100 percent aspartame. And indeed a few products such as Squirt, Sugar-Free Hires Root Beer and Sugar-Free Orange Crush, probably are using 100 percent aspartame to take advantage of its image as a safe, low calorie sweetener, according to Dr. Robert McQuate of the USDA.

Last summer the Center for Science in the Public Interest, a Washington, DC.-based health group, echoed Wurtman's concerns in a letter to the FDA which noted, "Our organization would like nothing more than to see saccharin, a carcinogen, replaced as quickly as possible. However, it would be most unfortunate if the replacement(s) had undesirable side effects." The center recommended that Searle be "required to submit to FDA thorough studies of aspartame's effects on neurotransmitter levels and human behavior immediately."

The FDA, however, dismissed Wurtman's concerns, concluding in a 15-page letter to him that it didn't believe "additional behavioral testing in animals or man was required prior to approving its use in soft drinks." The FDA has said Wurtman's "data do not support [his] hypothesis."

Searle's Robert Shapiro also argues that Wurtman's research is insuffient evidence that aspartame alone, or when consumed in combination with carbohydrates, may cause health risks. Dr. L.D. Stegnik, professor of pediatrics at the University of Iowa, who carried out a number of studies "with humans for Searle prior to FDA approval, adds, "There's a possibility Wurtman is right, but the probability is low."

But since the law says the burden of proof is on Searle to prove to a reasonable certainty that aspartame is safe, why not wait until Wurtman's hypothesis is tested? After all, the National Soft Drink Association stated in its draft objection to soft drink approval—which was never filed—that Wurtman's hypotheses could be "resolved conclusively" in "approximately six months."

"You can always ask one additional question," Shapiro said. "Has it been tested on left-handed shortstops on Thursday afternoons in the Tropic of Capricorn after midnight?"

He says Wurtman had an opportunity to make his case; the FDA concluded he was wrong. Shapiro says he has talked to "a hell of a lot of people—doctors, scientists, whom I respect"—who believe there was no valid reason to delay approval.

Wurtman told Common Cause Magazine that before aspartame was approved for soft drinks last summer, he discussed his concerns at an NSDA meeting. He also recalls running into Howard Roberts, the NSDA vice president for science and technology, at Washington's National Airport and telling Roberts that "if you and your constituents listen to the FDA, they'll be in a pack of trouble."

Wurtman says he has recently received funding to conduct further tests.

Will Americans Consume More Than the FDA Estimates?

The second major controversy involves questions about consumption levels. Use in soft drinks dramatically expands the availability of aspartame in the food supply. Several months after the FDA gave approval for aspartame use in soft drinks, Dr. William Pardridge, associate professor of medicine at the University of California, Los Angeles, wrote to the FDA, saying he believed it had "considerably" underestimated the consumption of aspartame.

The Community Nutrition Institute (CNI), represented by attorney James Turner, agrees and has gone to court seeking a hearing on the basis of this as well as other issues. Turner believes the FDA's underestimation of consumption levels "is

going to be at the core of any problems that emerge from now on."

The FDA agrees that "the projected estimates of aspartame consumption are central to the safety evaluation." In fact, in his 1981 decision approving aspartame for use in dry foods, former commissioner Hayes stated that "the safety assessment on the brain damage issues is tied closely to projected aspartame consumption levels."

In his decision, Hayes said the maximum projected consumption of aspartame is 34 milligrams a day per kilogram of body weight.

However, the National Soft Drink Association pointed out in a draft paper on aspartame use in soft drinks written last summer that a child weighing about 66 pounds would consume 23 milligrams of aspartame per kilogram of body weight by drinking 45 ounces of a drink flavored exclusively with aspartame. That means that a child who drank four cans of the soft drink in a day could be well on the way to hitting the FDA's maximum projected consumption.

Pardridge also believes it wouldn't be at all unusual for a person, particularly a child, to consume significantly more aspartame than the FDA estimates. In his letter to the FDA, he cites the hypothetical case of a 45-pound boy who eats a variety of aspartame-sweetened foods throughout day—cereal and orange drink for breakfast, another drink plus chocolate pudding for lunch. In the afternoon the child snacks on a soft drink and five sticks of chewing gum—all sweetened with aspartame.

Pardridge points out that the child will have consumed 31 milligrams of aspartame per kilogram before dinner, "where he might be confronted with aspartame-containing iced tea, chocolate milk, milk shakes, chocolate pudding pie, Jello, ice cream and numerous other products that will, no doubt, be created by an inventive aspartame cookery." He says it wouldn't be surprising if a child consumed 50 milligrams per kilogram of body weight in one day.

Therefore, "my question to the FDA is, what is the allowable daily intake of aspartame in milligrams per kilogram per day?"

Common Cause Magazine put that question to Sanford Miller, chief of the FDA's food safety division. He replied, "Oh, probably over 100 milligrams per kilogram. . . . I suppose we could go up to 100 milligrams per kilogram and still not have any of the faintest worries at all about what the consumption is. It's hard to pick a number and we picked a conservative one [34 milligrams per kilogram]."

He points out that the Joint Expert Committee on Food Additives, an advisory group to the World Health Organization, has recommended a higher maximum level, which is 40 milligrams per kilogram.

In his 1981 decision, Hayes said, "the available data establish" that the maximum projected consumption of 34 milligrams per kilogram is "still far, far below any level even suspected of being toxic."

So what is the toxic level? "That's hard to say," Miller observed. "In all the experiments that were done so far, including the short term human studies, no one's been able to find anyting of significance except some reduction in weight gain, which isn't surprising. . . . So a no effect level can be established at a variety of different levels. To answer your question, 'What's a toxic level?' that's hard to say."

But again, Hayes' decision stated that the "safety assessment on the brain damage issues is tied closely to projected aspartame consumption levels." So what's the level at which aspartame causes brain damage?

Miller says animal studies by Dr. John Olney, a critic of aspartame, didn't show brain lesions "until you get to very high levels," which he implied humans couldn't possibly reach.

While the FDA has said repeatedly it does not believe aspartame at projected levels of consumption could cause brain damage, Pardridge says "that is not the proper question." Instead, he says the FDA should have asked if high dose aspartame use would "cause subtile changes in brain development." He points to the possibility that women with a phenylalanine intolerance who consumed large quantities of aspartame while pregnant might give birth to infants with "a 10 to 15 percent drop" in expected IQ levels. He believes there "are 20 million individuals in the country with phenylalanine intolerance," many of whom may be unaware of their condition.

Pardridge recommended that the FDA restrict new products containing aspartame from entering the food supply "as soon as possible, until clinical and basic research allows for the reevaluation of the intended dosage and the norms for what constitutes a harmful effect of aspartame in humans."

ARE BREAKDOWN CHEMICALS SAFE?

The third controversy surrounds the decomposition of aspartame. When exposed to heat and acidic solutions, aspartame breaks down more rapidly and decomposes to chemicals such as DKP and methanol. The FDA has said that while aspartame loses some of its sweetness, there are no safety concerns.

But others, such as the Community Nutrition Institute (CNI), aren't as sure. The FDA acknowledges that aspartame breaks down in heat and/or acidic solutions but says, "any concern over possible toxic effects from DKP has been eliminated as a result of long term animal studies conducted using DKP itself as the test compound."

One of these studies, it's important to note, is the subject of a controversy of its own: A long term study to determine whether DKP causes brain tumors in rats was investigated by a 1977 FDA task force which concluded it was not certain that the rats ate the required amounts of DKP, thus possibly invalidating the test. Other FDA officials disagree, saying other evidence indicates the diet was homogeneous. This controversial long term test was one of the three tests examined at the 1980 Public Board of Inquiry to determine whether aspartame might cause cancer. (See main story for more on this controversy.)

Meanwhile, CNI and Dr. Woodrow Monte, director of the Food Science and Nutrition Laboratories at Arizona State University, charge that methyl alcohol, another breakdown product, may pose safety concerns for consumers. Monte says methyl alcohol's "chronic toxicity and carcinogenicity . . . have not been thoroughly investigated." Monte's criticisms, dismissed by Shapio as the equivalent of saying "the world is flat," have been widely reported, but Monte's outspoken criticisms of aspartame were undermined when it was revealed in *The Wall Street Journal* earlier this year that he and his lawyer allegedly had purchased "put" options on Searle stock shortly before Monte appeared on *The CBS Evening News* expressing his views. A "put" option enables the investor to profit if the stock value goes down.

DID THE SOFT DRINK INDUSTRY RESOLVE ITS SAFETY QUESTIONS?

According to a draft document obtained by Common Cause Magazine, the National Soft Drink Association (NSDA) considered filing an objection to the Food and Drug Administration's proposed approval of the use of aspartame in carbonated beverages. The draft objection was dated July 28, 1983, just two weeks before the deadline for filing formal objections.

In an interview, Dr. Robert McQuate, science director for the trade group, which represents franchise companies such as Coca-Cola and Pepsi as well as hundreds of individual bottlers, described the document as an "internal draft." He said the fact that the NSDA never filed the objection means the association resolved all the concerns it had raised in the draft objection about aspartame's safety. "I don't think it warrants a detailed defense," he said in response to questions about the document.

"The bottom line," McQuate says, "is that one, FDA approved the use of aspartame in carbonated beverages; and two, the soft drink industry has incorporated NutraSweet in about 70 percent of the diet soft drinks."

Nevertheless, the interview seemed to raise as many questions as it answered.

Neither McQuate nor Robert Shapiro, head of Searle's NutraSweet Group, who was also interviewed by Common Cause Magazine, fully explained what happened behind the scenes to turn the NSDA around. Both, however, hinted at significant maneuvering in the soft drink industry before NutraSweet was added to the soft drinks.

Shapiro, for example, scoffs at the suggestion that the industry ever had serious safety concerns. He and others suggest instead that the trade group was using the draft objection as a weapon during intense negotiations with Searle over, among other things, NutraSweet's cost. (Industry sources say Searle sells the sweetener for approximately $90 a pound; in contrast with saccharin, which costs less than $4 a pound.) As evidence, he points out that Searle and Coca-Cola thrashed out a "breakthrough agreement that defined the ground rules for NutraSweet use" close to the deadline for filing objections.

The NSDA draft petition outlines several concerns that echo criticisms made by others who think aspartame should not have been approved for soft drinks. The draft objection focuses primarily on two concerns: the instability of aspartame, which decomposes to chemicals such as DKP and methyl alcohol when in solution or exposed to heat; and concerns raised by Dr. Richard Wurtman, a professor of neuroendocrine regulation at the Massachusetts Institute of Technology (MIT). Wurtman says preliminary experiments indicate that large amounts of aspartame, especially when consumed with carbohydrates, may affect the brain's neurotransmitters and therefore behavior. The FDA and Searle disagree.

The draft objection states that Wurtman's questions are "significant because of the seriousness of the potential effects" and "because of aspartame's anticipated widespread use—use that includes consumption by potentially vulnerable sub-groups, such as children, pregnant women and hypertensives. Dr. Wurtman's concerns are shared by other distinguished scientists expert in this field." The draft objection also says the legal burden is on Searle to prove that there is a "reasonable certainty that no harm to human health will result form aspartame," and points out that it would be possible to resolve Wurtman's hypothesis "conclusively" within "approximately six months." The NSDA draft objection also says the FDA underestimated consumption of aspartame in soft drinks.

Why didn't the NSDA go forward with its objection based on the concerns raised by Wurtman?

McQuate says the issue was resolved by a 13-page response from the FDA to Wurtman saying his data didn't support his hypothesis.

Also during the interview, however, McQuate said the NSDA takes Wurtman's concerns "seriously." "I think there's a legitimate basis for his hypothesis. . . . I think it's worthy of further investigation."

Regarding the decomposition question, the draft objection states that Searle used an "inferior" analytical technique that "resulted in inadequate characterization of aspartame's decomposition products" and that there were "extensive deficiencies" in the stability studies. The draft objection also states that "under moderate conditions, extensive decomposition of aspartame may occur in soft drinks," yet Searle is unable to account for more than one third of the chemicals to which aspartame decomposes. Therefore, "judgments about the safety of aspartame in soft drinks cannot be made confidently."

How did NSDA resolve the decomposition question?

McQuate says the decomposition question was resolved when one or more of the soft drink companies did their own studies last summer that demonstrated "the breakdown would not be hazardous."

McQuate acknowledges that the studies were short term. Long term studies that might shed light on the potential effects of long term exposure to aspartame's unidentified breakdown products were not done "because that obviously would take two years just to conduct, let alone evaluate the results," McQuate says.

Have the soft drink companies made the short term studies available to the public? No, McQuate says, adding he doubts these studies would satisfy critics such as consumer attorney James Turner, who he suggests would never be satisfied with any study. Why provide "fodder" for critics? he asked. "I don't think it's in our best interest [to make the studies public]. It becomes another issue we have to defend."

If NutraSweet is safe, why aren't all the soft drink companies using 100 percent NutraSweet instead of a blend of NutraSweet and saccharin, since saccharin is known to cause cancer in rats?

McQuate says there are two reasons. First, aspartame is much more expensive than saccharin. Second, NutraSweet is known to lose its sweetness when exposed to high temperatures. Therefore, soft drinks which aren't sold expeditiously could lose sweetness and "you will have an unacceptable product."

He says he believes that companies which are using 100 percent NutraSweet—such as Squirt—are doing so as a marketing strategy that takes advantage of a public perception that saccharin isn't safe. So how has Squirt resolved the concern that aspartame breaks down in heat and loses sweetness? Squirt representatives refused to return phone calls.

Finally, McQuate won't acknowledge that saccharin isn't safe, only that it "has been shown to produce bladder cancer in male rats at high [dosage] levels."

(In 1977 the FDA proposed banning the use of saccharin in food and beverages. In response to public pressure, however, Congress said it could be used.)

Why haven't studies been done to determine the synergistic (combined) effects, if any, of blending saccharin and aspartame?

"It's a good question," McQuate answered. "I am not sure that the technology is there to do that . . . . Maybe it could be done, but I don't think it would be a simple design of an experiment. I guess, in general, you've got me thinking it's a good question."

Has Searle conducted such studies? "That's an interesting question," Shapiro said. "I don't think so. In fact, it's the first time I've ever heard that question raised."

Notwithstanding the draft objection, Shapiro insists that NSDA never had serious concerns about safety. Instead, he says, the soft drink companies were worried about the high price of aspartame and the fact that its instability might cause some drinks to lose sweetness before they were sold. The instability "poses no safety issue whatever, but it does pose a product quality issue," Shapiro says.

He also acknowledges that Searle, which owns the patent on both NutraSweet and the NutraSweet-saccharin blend, was reluctant to let companies use the blend in part because of fears that consumers who first tested the blend would decide, "'Hey, I don't like NutraSweet,' when in fact they really would like NutraSweet—it's the saccharin they don't like."

A high level FDA official says Searle was trying to force the soft drink companies to use 100 percent NutraSweet, and in addition Searle wanted the companies to sign long term contracts that featured regular price escalations.

So, would it be accurate to say that Searle wanted the soft drink companies to use 100 percent NutraSweet, but they balked because of the cost, and therefore used the threat of filing an objection to stop the approval as leverage in negotiations?

"You're inferring to much," Shapiro says. "I can only say that if you were to ask people in the soft drink industry whether they have concerns as to the safety of NutraSweet as used in their product, I think the answer very clearly is no.' They have been through that kind of agony in the past," he says, referring to cyclamates, which the FDA banned in 1970, and saccharin, which FDA proposed banning in 1977. "They are not eager to go through that process again."

Does NutraSweet Cause Adverse Reactions?

In an affidavit filed in a U.S. district court last January, a woman named "Jacqueline" stated that her four-year-old son Stephen had had numerous adverse reactions to aspartame (NutraSweet)—among them headaches, uncontrollable behavior and slurred speech. The woman, whose full name was deleted in the affidavit to protect her privacy, said she had given Stephen various aspartame-sweetened products, among them Kool-Aid and Wyler's Lemonade.

Her affidavit stated that her doctor concurred that aspartame was the cause of Stephen's "aberrational behavior and symptoms," and she concluded by expressing her concern that it would be hard for Stephen, "and other children who cannot read labels for contents," to avoid exposure to aspartame in the future.

As of June the FDA acknowledged receiving about 600 complaints (most of them this year) from consumers across the country who believe they have had adverse reactions to aspartame. These complaints, which experts refer to as "anecdotal," did not follow a pattern, the FDA maintained. However, taking a step it describes as "unusual," the FDA forwarded the complaints to the Centers for Disease Control (CDC) in Atlanta, which carries out epidemiological research for the federal government. The FDA says it "hopes" the CDC's investigation will be completed this July. "We are looking at this very, very carefully," says Sanford Miller, who heads the FDA's food safety division. "We take these [complaints] very seriously.

Copies of many of the complaints, along with complaints received by Searle and by MIT scientist Dr. Richard Wurtman, were obtained from FDA by Common Cause Magazine under the Freedom of Information Act. They cite symptoms ranging from headaches, dizziness and insomnia to numbness, rashes, menstrual problems and nausea.

It is obviously harder for a person to detect a reaction to a food additive than to a prescription drug, but a number of people filing complaints said that to be certain in their own minds, they had tested their reactions by stopping their consumption and then starting it again to see whether the symptoms reappeared.

An August 1983 letter to Wurtman stated that about a half-hour after consuming an aspartame-sweetened drink made from a powdered mix, the writer "suddenly felt slightly dizzy and could not concentrate on what I was reading. The skin on my face felt itchy and my ears began to ring. . . . My heart was beating quite rapidly and I had a burning sensation in my chest. This episode lasted for about one hour." The consumer acknowledged also taking a medication called Dyazide, but said the adverse reaction had "never happened to me before, nor has it happened since" last consuming aspartame.

A mother wrote that her son broke out in hives two hours after drinking aspartame-sweetened Kool-Aid . . . A man reported that he experienced headaches, dizziness and irritability after drinking five to six bottles a day of diet soda. . . . A diabetic reported that after using four packets of Equal powder he "broke out in quarter-sized, red blotches on chest, arms and hips." . . . And another person wrote that after using Equal "I started to have waves of numbness and tingly feelings in my head." After discontinuing use of the product, the person wrote, the symptoms disappeared.

People started to write to MIT's Wurtman after he began to appear in various media reports on aspartame. Wurtman, who told the FDA in February he had received "well over 1,000" letters and "related communications" from consumers, pointed out that "most of these letters have lacked creditibility and have been discarded. However, an important number have described symptoms which seemed to bear a relationship to aspartame consumption, and which were compatible with what might be expected after an increase in brain phenylalanine levels." Phenylalanine, an amino acid, is one of the major components of aspartame. Wurtman had done some experiments which he believes indicate that large amounts of aspartame—especially when consumed with foods containing carbohydrates—may affect behavior.

Consumer attorney James Turner, who represents the Community Nutrition Institute, a public interest group, points out that a number of complaints correspond to symptoms reported in one Searle test on humans. He says the study "reported five times as many complaints by aspartame users than by the control group, including complaints of menstrual cramps, vaginal spotting, depression, alteration of menses, headaches, appetite increase and weight gain."

But the FDA says Turner is taking the study's results out of context: "The clinical study referred to . . . was only one of several clinical studies, which included normal adults and children, as well as obese and diabetic adults, conducted by [Searle] and submitted to the agency in support of its petition on dry uses of aspartame," the agency stated in turning down one of Turner's requests for a public hearing on aspartame's safety. It added, "based on an analysis of the results from all these studies, FDA con-

cluded that there was no evidence of any consistent or obvious pattern of specific complaints from aspartame use."

Searle executive Robert Shapiro agrees with the FDA that the results of that test were not statistically significant and says he doesn't believe the complaints were related to aspartame use. Both Shapiro and the FDA's Miller point out that it's worth noting that in Canada, where aspartame has been used for three years, few people have complained to Canada's health officials. They both say that Searle's mass advertising campaign promoting NutraSweet and the media attention regarding the product and its alleged problems may have led people to believe their symptoms were associated with NutraSweet. In an interview Shapiro remarked, "I believe if we were to introduce lettuce to the market tomorrow with a big national publicity campaign, and nobody had ever seen lettuce before, and people started eating lettuce, my guess is you would get exactly the same kinds of complaints."

Shapiro readily acknowledges, however, that if there were a problem with a food product, an individual probably wouldn't know to associate a given symptom with it unless made aware of the possible connection.

By December 1983, Wurtman wrote to the FDA saying he had "received enough letters describing what may be seizures after a high dose aspartame consumption that I think you all ought to look into it systematically."

Consumer attorney Turner points out that in an experiment submitted by Searle in the early 1970s, all monkeys receiving aspartame in medium and high doses experienced grand mal seizures. FDA scientists reviewing the study in 1973 said in documents obtained by Common Cause Magazine that it was unfortunate the monkeys had not been purchased by Searle so that they could be killed and their nervous systems examined in order to learn more about the seizures. Although Searle had implied in its report to the FDA that the monkeys were unavailable for purchase, a team of FDA investigators later said this was untrue. The monkeys had been available; Searle chose not to buy them.

FDA officials were so concerned about this omission that it helped form the basis of a 1977 FDA request for a grand jury investigation of Searle. The letter requesting a grand jury stated that Searle used "very great literary license in drafting its report" on the monkey study and alleged that Searle had made "four false statements and entries" in the report.

The letter also alleged that it was "more likely" that Searle didn't buy the animals because "no post-mortem comparative data" were available, saying, "if Searle had found adverse effects, it would have had no way to show that the consequences were not attributable to aspartame. Searle did not want to take this chance." The grand jury probe was later dropped.

Searle and the FDA now agree that the monkey study was poorly designed and run and therefore invalid. In documents submitted to the 1980 Public Board of Inquiry, which reviewed aspartame, the FDA said it did not need to rely on the monkey study, which it had described in 1975 as "pivotal," in its safety evaluation. Meanwhile Searle had commissioned another monkey study; these monkeys did not have seizures. While the FDA acknowledged at the Public Board of Inquiry that it had not subjected this study "to detailed review," it nevertheless concluded, "none of the experimental animals showed abnormal EEGs (readings of electrical activity in the brain) or seizures."

But Turner is still not satisfied. He believes the second test did not fully account for seizures in the first test and that a third test should have been done for assurance. He has argued that even if you granted that the study was poorly run, the fact that the monkeys had seizures is reason for concern. The FDA and Searle disagree.

Wurtman also believes a third study should have been done before resolving the question, although, "its sort of academic now. It's getting warm again and consumption is much greater on a hot day in August than a cold day in January." Given the increased consumption this summer, Wurtman says if there is a correlation between aspartame consumption and various complaints, "we'll know." How will we know? "If relatively large numbers of people have unpleasant experiences with neurologic functions," Wurtman responds.

Wurtman hastens to add, "I can't say if there is a problem; I can't say there isn't. But it's unfortunate to experiment on people."

He says he hopes doctors will ask patients about their aspartame consumption. Searle sent out information kits to 200,000 doctors assuring them of aspartame's safety.

Shapiro says he is "not prepared to say . . . in the absence of examining people" that a product containing aspartame might have caused a certain symptom, and "I'm certainly not prepared to say it was caused by the aspartame." (In other words, the symptom may have been caused by something else in the product.)

However, Shapiro says, "In the case of any serious complaints, you would want to do a medical workup. I am prepared to pick an independent outside science center and pay the cost of somebody getting examined to find out in fact if there is some population group which has some reactions I'd want to know about."

[Committee Report]

XII. Additional Views of Senator Howard M. Metzenbaum on S. 484

On April 2, the Labor Committee held an extensive hearing on three low-calorie, non-nutritive sweeteners: saccharin, aspartame (NutraSweet) and cyclamate. The hearing was held to assist the Committee in its deliberations on S. 484, a bill to amend the Saccharin Study and Labeling Act.

It was clear from the outset that the issues of science and safety surrounding the three sweeteners were inextricably entwined. The justification for the moratorium on the saccharin ban proposed by the FDA in 1977 had always been the fact that there were no substitutes for saccharin's principal uses. Since the introduction of aspartame (NutraSweet) in 1981, and its approval for use in soft drinks in 1983, that situation has clearly changed. The FDA's current review of cyclamate is also a key component of the artificial sweetener "equation" and one more reason that it is impossible to consider in isolation the issues of health and safety surrounding these substances.

As a result of the hearing, a number of issues became clear. First, regarding saccharin:

In 1977, the FDA estimated that saccharin could cause up to 1,200 additional cases of bladder cancer a year, assuming everyone in the U.S. consumed the saccharin equivalent of one diet soda a day. The FDA still stands by that assessment.

Two recent studies on saccharin as a carcinogen and a co-carcinogen (or cancer promoter) show the substance produces tumors in the rat at lower doses than those in the 1977 tests. The FDA used these 1977 tests to justify its proposed ban on saccharin as a food additive.

The Canadian government has seen no new evidence to cause it to reconsider its decision in 1977 to ban saccharin as a food additive in foods and soft drinks.

If the current saccharin legislation lapsed for a period of time, the product would remain on the market. The FDA Commissioner testified that, "with the most rapid action, it is 180 days to a year" before any action would be taken to remove saccharin from the market.

The original Saccharin Information and Labeling Act required warnings on products containing saccharin. These warnings cite the link between saccharin and cancer in laboratory animals. The law states:

Such statement shall be located in a conspicuous place on such label, and labeling as proximate as possible to the name of such food shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter.

It is clear that this provision of the law is being ignored. Report language acompanying this bill directs the FDA to examine the efficacy of these warnings and report to Congress on how the law is being obeyed.

Regarding cyclamate, the FDA is currently undertaking a review of the carcinogenicity of this substance. Concern had been expressed that the FDA was not going to give full consideration to other problems associated with cyclamate, i.e., testicular atrophy and genetic damage. The FDA Commissioner testified that the FDA intends to examine these issues fully and that it could be up to three years before any decision is made.

In addition, a number of concerns regarding aspartame (NutraSweet) were raised at the hearing on April 2. In July, 1984, Common Cause published an extensive investigative report on the manner in which the FDA approved aspartame. The highlights of that report include the following:

In 1977, the FDA recommended that Searle be brought before a grand jury for fraudulent tests including tests on aspartame.

The FDA Commissioner in office when aspartame was approved rejected the findings of a Scientific Board of Inquiry that recommended that aspartame not be approved pending further tests on brain tumors.

The FDA Commissioner's own in-house team of scientists split on the issue of aspartame approval. Three of the six scientists recommended against approval

Those who say there is no reason to be concerned about the safety of NutraSweet point to a recent study of consumer complaints carried out by the Center for Disease Control. Though the CDC concluded that the consumer complaints provided no cause for removing NutraSweet from the market, they did suggest further studies in their report:

"The number of instances of persons challenging themselves several times with aspartame-containing products and reporting symptoms with each rechallenge suggests that some individuals may be sensitive. The only way to clearly determine this is through focused clinical studies. Because of the numbers of reports, the subjety and potential seriousness of some of the manifestations, the concerns of some scientists, and the possibility that one complainant has had his symptoms of hyperactivity verified on independent exam, it would seem that the highest priority for any future investigations might be in the neurological/behavioral area, focusing on such symptoms as

headaches, mood alterations, and behavior changes."

The report language accompanying this bill directs the FDA to ensure that these tests are undertaken.

At mark up, I proposed an amendment which would require the manufacturers of diet soft drinks to include on their label how much aspartame (NutraSweet) each serving contains.

I believe consumers have a right to this information given the questions which have been raised about NutraSweet and the extraordinary increase in consumption levels of this product since its introduction in 1981 (last year per capita consumption increased 66%).

The National Soft Drink Association has lobbied strongly against this proposal. However, this is the same association which, in 1983, prepared a draft legal document objecting to NutraSweet's being allowed on the market, citing serious and unresolved questions about the public health. Though that document was not filed, it indicates the organization had significant health concerns relating to the amount of aspartame consumed before this product was approved for soft drinks. The following quotes are from a document entitled "Objections of the National Soft Drink Association to a Final Rule Permitting the Use of Aspartame in Carbonated Beverages and Carbonated Beverage Syrup Bases and a Request for a Hearing on the Objections." The document is dated August 8, 1983, and was prepared by Patton, Boggs and Blow and the General Counsel for the National Soft Drink Association:

"G. D. Searle and Company has not demonstrated to a reasonable certainty that the use of aspartame in soft drinks, without quantitative limitation, will not adversely affect human health as a result of the changes such use is likely to cause in brain chemistry and under certain reasonably anticipated conditions of use."

"For these reasons, Searle has not met its burden of demonstrating to a reasonable certainty that the unlimited use of aspartame, especially in combination with carbohydrates, will not adversely affect human health. The questions posed by Dr. Wurtman are significant because of the seriousness of the potential effects (e.g., changes in blood pressure) and because of aspartame's anticipated widespread use—use that includes consumption by potentially vulnerable sub-groups, such as children, pregnant women, and hypertensives."

"Specifically, Searle has not met its burdens under section 409 . . . to demonstrate that aspartame is safe and functional for use in soft drinks."

"Collectively, the extensive deficiencies in the stability studies conducted by Searle to demonstrate that aspartame and its degradation products are safe in soft drinks intended to be sold in the United States, render those studies inadequate and unreliable."

There have been hundreds of reports from consumers around the country suggesting a possible relationship between their consumption of NutraSweet and subsequent symptoms including headaches, aberrational behavior, slurred speech, etc.

During the Labor Committee hearing on saccharin, NutraSweet, and cyclamate held on April 2, Dr. Richard Wurtman of M.I.T., testified as follows:

"The problem at present is that it is difficult if not impossible for the patient or his physician to know how much aspartame it contains . . . I believe it is essential that companies which include aspartame in their products be required to indicate on the labels (in readable print) how much of the sweetener is present in each can or serving. This simple change in labeling practice would, I believe, sharply reduce the number of consumers who believe without probable foundation that they have suffered aspartame-related side-effects. Perhaps more importantly, it would also enable physicians to identify those patients who might really have had such responses, so that such people might then undergo controlled clinical testing."

Since 1981, the FDA has attached an ADI (acceptable maximum daily intake) to NutraSweet. That ADI is currently 50 milligrams per kilogram of body weight. While an adult weighing 154 pounds would not meet that limit before he consumed 5 liters of diet soft drink, a four-year-old weighing 25 pounds would hit that limit at three cans of diet soda. Consumers have no way of knowing if they have reached the FDA limit without knowing how much is in the can. Ideally, we should have the ADI on the can as well, but it will take some time to figure out how that could be done effectively. In the meantime we should ensure that the quantity is on the label. We must start somewhere, and this is an important first step.

Many questions must be resolved concerning aspartame. The FDA should take an active role to ensure that tests are conducted to determine whether individuals, particularly children, are likely to experience side-effects from NutraSweet at current and projected consumption levels. The FDA should also run tests on how NutraSweet affects those who might be taking different types of medication.

Finally, given the serious questions which remain regarding the FDA approval process for NutraSweet, the FDA should ensure that certain key pivotal animal tests are repeated. Only when all of these questions are resolved can consumers be certain that they are receiving the full protection provided by our food and drug laws.

EXHIBIT 1

OBJECTIONS OF THE NATIONAL SOFT DRINK ASSOCIATION TO A FINAL RULE PERMITTING THE USE OF ASPARTAME IN CARBONATED BEVERAGES AND CARBONATED BEVERAGE SYRUP BASES AND A REQUEST FOR A HEARING ON THE OBJECTIONS.

(Docket No. 82F-0305)

DRAFT: JULY 26, 1983

Objection One: Searle has not demonstrated to a reasonable certainty that aspartame and its degradation products are safe for use in soft drinks. Without quantitative limitation, under temperature conditions likely to prevail in the United States.

SUMMARY OF BASIS FOR OBJECTION

Aspartame is inherently, markedly and uniquely unstable in aqueous media. In a liquid, such as a soft drink, APM will degrade as a function of temperature and pH. Higher temperatures and more acidic liquids increase the rate of degradation. Higher temperatures may also affect the degradation products which are formed. Given the circumstance of APM's unusual instability, reliable and comprehensive analyses of APM's degradation in soft drinks—both as to the rate of degradation (and the subsequent loss of sweetness) and to the confirmed identification of the major degradation products—is crucial to establish the safety of the use of APM. Without adequate identification of AMP's significant decomposition products, it is not possible to find, to a reasonable certainty, that APM is safe. The data and information submitted by Searle in support of its petition to amend 21 C.F.R. § 172.804 to permit APM use in soft drinks, however, do not demonstrate that APM is safe for use in soft drinks. These data are insufficient to establish safety because the petition lacks comprehensive, reliable and accurate analytical data on APM and the products "adversely affected" by the issuance of the regulation authorizing the use of aspartame ("APM") in soft drinks. As the national trade association representing the soft drink industry in this country, NSDA's member soft drink manufacturers and soft drink franchisers are directly and immediately affected by the issuance of a regulation which authorizes the use of a new sweetener in its products. Approximately seventy-six percent of the nation's 1600 soft drink manufacturers are active members of the Association. These members account for more than ninety percent of the soft drink production in this country. In addition, the vast majority of soft drink franchisers which manufacturer the concentrates and syrups from which soft drinks are made are associate members of the Association.

II. SUMMARY OF BASIS FOR THE OBJECTIONS

[To be added].

OBJECTIONS OF THE NATIONAL SOFT DRINK ASSOCIATION TO THE ISSUANCE BY THE FOOD AND DRUG ADMINISTRATION OF A REGULATION (21 C.F.R. § 172.804) TO AUTHORIZE THE USE OF ASPARTAME IN CARBONATED BEVERAGES AND CARBONATED BEVERAGE BASES

In the Federal Register of July 8, 1983 (48 Fed. Reg. 31376), the Food and Drug Administration ("FDA") issued a regulation amending section 172.804 of its regulations, 21 C.F.R. § 172.804, to authorize the use of aspartame in carbonated beverages and carbonated beverage bases (collectively referred to as "soft drinks"). This action was taken in response to a food additive petition (FAP 2A3661) filed on October 15, 1982 by the Searle Research and Development Division of the G.D. Searle Co. ("Searle").

In these objections, NSDA demonstrates that there exist genuine and substantial issues of fact material to FDA's amendment of its regulations to permit aspartame use in soft drinks. Specifically, Searle has not met its burdens under section 409 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 348 ("FDC Act") to demonstrate that aspartame is safe and functional for use in soft drinks. NSDA therefore objects to the Commissioner's order amending 21 C.F.R. § 172.804 and requests that a hearing as provided under section 409(f) of the FDC Act, 21 U.S.C. § 348(f) be convened.

NSDA is a party that is, within the meaning of section 409(f)(1) of the FDC Act, 21 U.S.C. § 348(f)(1), methyl ester (PM) and beta-aspartame (beta-APM).[1] (Searle FAP at 13) Only in the cases of APM and DKP did Searle use high pressure liquid chromotography (HPLC). For the other four known principal breakdown products, Searle used thin-layer chromotography (TLC).

HPLC is a far superior analytical method relative to TLC (cites) and numerous HPLC methods exist for the detection and quantification of amino acids (cites. Searle's choice of TLC over HPLC adversely affected the quality and type of analytical data generated on APM and its decomposition products in soft drinks. The unfortunate and inexpli-

[1] The importance of comprehensive and reliable analyses of APM's decomposition products is demonstrated by the fact that based on the chemical structure of APM, one would not expect PM or beta-APM to be degradation products. Indeed, initially Searle did not look for either one. Other unexpected decomposition products of unproven safety could, of course, also be present when APM degrades.

cable choice [8] of an inferior analytical technique, when superior and recognized methods are available, has resulted in inadequate characterization of APM's decomposition products.

HPLC is a practicable, well-accepted analytical method[9] which is commonly employed by FDA. When the safety and suitability for use of a food additive such as APM with an acknowledged degradation problem (and anticipated high consumption) is under evaluation, HPLC is clearly the analytical method of choice.

TLC, on the other hand, produces good qualitative results, but is, at best, only semi-quantitative, since the quantification used is based on visual comparisons of spot sizes and intensities. (cite) Indeed, Searle itself has acknowledged the inadequacy of the analytical method that it chose, when it described, in the petition, the quantity of degradation products identified using TLC as "estimates." (cite)

The inappropriateness of using TLC as a principal analytical method is compounded by the fact that the values of APM degradation products being measured are close to the limits of detection of the method (cite).[10] Thus, the values purportedly obtained by the TLC method cannot be considered to be very precise. Finally, an important decomposition product of APM, aspartic acid (AA) cannot be detected at all using TLC.

In short, for reasons which are not apparent, the petitioner chose to use a semi-quantitative analytical method to analyze for numerous major APM breakdown products close to the limits of detection, when that method is not the best method available. The quality of the analytical data presented are, therefore, substantially inferior to those which could have reasonably been obtained.

(b) The Searle Analyses for APM Decomposition Products are Deficient.

Aside from its choice of TLC over HPLC, the analyses conducted by the petitioner to identify and quantify the breakdown products of APM in soft drinks are plagued by numerous significant deficiencies which result in clear and unmistakeable inadequacies in the detection and quantification of the major decomposition products of APM in soft drinks. In the face of these deficiencies, Searle has not reasonably identified substances formed in soft drinks because of the use of APM, as required under section 409(c)(5)(A) of the FDC Act, 21 U.S.C. § 348(c)(5)(A). The safety of this use of APM cannot be said to have been shown to a reasonable certainty in the face of these inadequacies.

There are at least six significant deficiencies in the HPLC analyses undertaken by Searle to identify and quantify APM and DKP in soft drinks:

(a) The standards for use of HPLC to detect APM and DKP were prepared in buffered aqueous solutions. A far better technique would have been to prepare the standards using beverage matrices. The use of beverage matrices would have reduced the danger of interfering compounds coeluting with the compound of interest.

(b) Searle does not appear to have submitted to FDA to HPLC chromatograms of the blanks (unsweetened beverages); without these chromatograms, the results obtained in sweetened beverages cannot be evaluated.

(c) The chromatograms of the beverages which were submitted by Searle contain peaks which can cause difficulties with quantification. For example, the DKP in the root beer chromatograms is badly overlapped by another peak.

(d) No recovery data for DKP were presented and the precision of the DKP concentrations was only determined for standard solutions.

(e) The purity of the initial APM was not established, although it can contain at least five percent impurities, as calculated from the zero time values in Searle's studies.

(f) Searle analyzed only single bottles at any given time and temperature. This aspect of the study design fails to account for anticipated bottle-to-bottle variations. Single bottle analytical data cannot, under any circumstances, amount to a comprehensive and reliable characterization of the decomposition products of an additive with a well-known instability problem.

Likewise, the TLC analyses are deficient (these deficiencies are in addition to the inherent limitations of the TLC method):

(a) Standards for the TLC analyses were prepared in distilled water. As in the case of the HPLC analyses, the better technique would have been to prepare them in beverage matrices.

(b) Searle did not submit (and apparently did not attempt) any recovery or precision data for its TLC analyses.

(c) In the TLC analyses, only single aliquots of single bottles were analyzed at any given time and temperature, thus rendering the putative quantitative results inherently unreliable.

(d) Measurable levels of beta-APM and PM may have existed in the starting material, but were not quantified at the beginning of the analyses (presumably because they were unexpected decomposition products). Moreover, it is unclear from Searle's data how the spots on the TLC plates were identified. If, as appears to be the case, identification was based solely on the comparison of R, values, the identifications can only be called tentative. Confirmation of the identifications by spectroscopic methods should have been undertaken. The failure to confirm these identifications undermines many of the major assumptions made by Searle throughout its analytical studies.

Collectively, the extensive deficiencies in the stability studies conducted by Searle to demonstrate that APM and its degradation products are safe in soft drinks intended to be sold in the United States, render those studies inadequate and unreliable. It is not possible on the basis of these studies to conclude that the petitioner has demonstrated that, notwithstanding its inherent instability, APM is safe for use in soft drinks. The failure of proof by Searle is even more evident, as is shown in the following section of these objections, when one considers the extent to which the decomposition products of APM in soft drinks are not known or identified.

(c) APM Decomposes Extensively in Soft Drinks Under Moderate Conditions, But Searle's Data Fail to Identify Adequately the Decomposition Products.

Notwithstanding the multiple and serious deficiencies in the stability studies conducted on APM in soft drinks, one conclusion does emerge: under moderate conditions, extensive decomposition of APM may occur in soft drinks. Moreover, a substantial portion of the decomposition products are not known. APM cannot be considered to be shown to be safe for use in soft drinks when the results of its known decomposition phenomenon—marked breakdown in liquid beverages—are not well identified.

For example, in the Searle studies, a cola beverage was kept at 30°C (86°F) for 40 weeks. (cite) In analyses conducted at that time, only fifty (50) percent (weight basis) of the original starting material was found.[11] Even if one accepts one of Searle's main assumptions about APM decomposition in soft drinks—that is, that aspartic acid (AA) is formed in amounts equal to the PHE and PM (mole basis) and that methanol is formed in amounts equal to the DKP, AP and PHE (mole basis) (cite)—the percent recovery of the original material is only increased to sixty-four (64) percent.[12] Thus, even when viewed most favorably, the analyses fail to account for over one-third of the original material.

This startling deficiency in the stability studies is further demonstrated by this table, also drawn from Searle data of beverages stored at 30°C (86°F), which illustrates the material balances obtained: [13]

* * * * *

The inability to account for as much as thirty-nine (39) percent of APM's decomposition products is significant. With such a high unknown factor, judgments about the safety of APM in soft drinks cannot be made confidently. Possible explanations for, and speculation about, the material balance discrepancies abound: secondary reactions may be occurring (possibly with the flavor components in the beverages); additional, but unidentified decomposition products may exist (as occurred in the case of Pm and beta-APM); or the inaccuracy and inadequacies of the analytical methods may account for the gaps in the data. No explanation for the discrepencies in material balances—that is, for the high percentage of unknown material—can, however, be supported on the basis of the data submitted by Searle. The significance of the unknown decomposition products simply cannot be determined in the absence of complete, careful, and reliable analyses—analyses which are not currently available because the petitioner failed to conduct or submit them.[14]

2. Searle Has Not Characterized The Decomposition Products of APM in Soft Drinks Under Temperature Conditions To Which The Beverages Are Likely To Be Exposed In the United States.

A suitable assessment of the stability of APM in soft drinks can be conducted. Such

[8] The availability of HPLC to detect and quantify APM's decomposition products is demonstrated by, among other things, a paper presented by three representatives of Searle. (LeVon, Mazur and Ripper, "Aspartame (APM) as a Sweetener In Carbonated Soft Drinks") (Appendix). In that paper, Searle stated that HPLC was currently used to detect APM, DKP and AP and PHE. Nevertheless, the petition does not contain HPLC-generated data for AP or PHE.

[9] Section 171.1(c) of the agency's regulations, 21 C.F.R. § 171.1(c), requires that an analytical method for detection of a food additive and substances formed in or on food because of its use be practicable and one which "can be applied with consistent results by any properly equipped and trained laboratory personnel." HPLC is clearly such a method.

[10] See examples

[11] This figure is derived as follows from Searle data: 13 percent AOM, 21 percent DKP, 3 percent AP, 8 percent PHE, and 5 percent PM.

[12] The increase comes from 10 percent AA and 4 percent methanol.

[13] A material balance accounts for the quality of the starting material, the quantity of identified decomposition products (or by-products, reaction products etc.) and the quantity of unknown material. Because of the inadequacies in the analyses documented in section — above, the figures in this table may be inaccurate. Nevertheless, the discrepancies in the material balance raise the possibility of significant unknown decomposition products.

[14] A tempting, but unsatisfactory, resolution of the material balance discrepancy is to assume that the safety of the decomposition products were determined in the chronic studies in laboratory animals which Searle conducted. This putative resolution does not hold, however, because these degradation products would not have undergone testing, since the APM in the feeding regimen was in freshly prepared doses.

an assessment would necessarily involve the use of sample beverages in a variety of flavors and varying pH, and, most importantly, involve exposure of the beverages to temperature conditions which approximate those which are reasonably expected to occur in practice (or under conditions which permit reasonable projections to be made to actual conditions).[9] Unless the sample APM-sweetened beverages are exposed to realistic temperature conditions, the temperature-sensitive degradation characteristics of APM, and in particular its potentially significant decomposition products, cannot be known. The data submitted by Searle are not derived from appropriate test conditions. Judgments about the extent of APM instability and its degradation products in soft drinks under actual conditions of use cannot, therefore, be inferred from the limited laboratory data.

To assess APM's instability in soft drinks, Searle exposed bottles of ready-to-drink beverages in four flavors (cola, root beer, lemon-lime and orange) to consistent temperatures of 55°, 40, 30, 20 and 5°C.[10] According to Searle's petition, "[I]n each flavor a loss of APM occurred with the rate of degradation directly related to the storage temperature for the carbonated beverages. The rate of APM loss from beverages was pH dependent." Moreover, Searle noted that "as the temperature increases, the rate of degradation becomes more pronounced."[11] Some of the effects on APM degradation in soft drinks are illustrated in a table in the Searle petition.[12] In that table, for example, after 20 weeks at 30°C (86°F), a beverage with a pH between 2.5 and 3.0, contained less than 40 percent of the original amount of APM. For beverages with similar pH, but kept at 40°C (104°F) for 20 weeks, less than ten percent of the original APM remained. Less pronounced degradation is seen at higher pH and/or at lower temperatures.

Although these stability tests show significant degradation of APM at consistent temperatures over relatively short time periods, they shed virtually no light on the probable degradation rate and products for soft drinks exposed to a variety of temperatures—including temperatures higher than any used in Searle's studies—during storage, handling, sale and use, temperatures which are known to occur and to which soft drinks are known to be exposed. Without stability studies conducted under such conditions, APM cannot be said to be appropriately stable in soft drinks, nor can its degradation products be considered to be adequately identified (assuming that analytical techniques were used which would yield complete and reliable results) nor can it be considered to have been shown to be safe.

The range of temperature conditions to which soft drinks are exposed during the summer months in the southern United States[13] is illustrated by a study conducted by the Coca-Cola Company's Corporate Packaging Department in 1976 and submitted to the Consumer Product Safety Commission.[14] That study shows that during the summer months, soft drinks are often exposed to relatively high temperatures for certain time periods in the course of distribution from the bottling plant to the consumer. High temperatures do, of course, routinely occur in much of the United States, including the southern regions; conditions of storage and distribution for soft drinks can elevate these temperatures significantly.

In summary, the study assessed: (1) warehouse temperatures in Marietta, Georgia and Wichita Falls, Texas; (2) route truck temperatures in Wichita Falls; (3) full sun and outside ambient temperatures in Wichita Falls;[15] and (4) parked car temperatures in Atlanta, Georgia and Wichita Falls. Each of these test environments is known to occur in practice and the tests were performed under actual, as opposed to laboratory, conditions.

Several significant conclusions can be drawn from this study. First, in those situations where the bottled beverage is heated only by conduction from the surrounding air (shaded location in a warehouse or in an automobile trunk parked indoors) the ratio of product temperature to the temperature of the surrounding air would be 0.92 to 0.94. In enclosed environments exposed to sunlight, however, ratios much greater than one would be expected. For example, a ratio of product temperature to air temperature of 1.45 was found for a test car parked in full sunlight. In other situations where sunlight was a direct heating factor (e.g., open air service station promotions or open bay delivery trucks) typical ratios were 1.10 to 1.15.

The effects of these ratios on product temperature are demonstrated by using summer temperatures for Phoenix, Arizona, where the average daily high in July is 40°C (104°F). During July in Phoenix, a soft drink in full sunlight could reach a temperature of 49°C (120°F) (104° x 1.15). The same product in a car parked in full sunlight could reach 66°C (151°F) (104°F x 1.45)[16]; soft drinks in a warehouse with an ambient temperature of 110° could reach temperatures of 38°C (101°F) to 39°C (103°F) (0.92-0.94 x. 110°F).

Overall, the study, considered together with representative historical temperature data (Appendix ——) show that soft drinks will frequently be exposed to temperatures of 32°C (90°F) to 49°C (120°F). In some cases product temperatures as high as 66°C (151°F) (especially in the southwestern United States) can be reached.

The effects of these high product temperatures on APM degradation and the formation of degradation products, and the effects of temperature variation (for example, soft drinks displayed at a service station may reach temperatures of 49°C (120°F) for most of the afternoon, drop in temperature overnight, and heat up again during the following day) cannot be determined from the data submitted by Searle to the FDA.

What those data do suggest, however, is that significant APM degradation at high temperatures occurs within a short period of time. For example, in Searle's stability tests, an orange beverage held at 40 °C (104 °F) (average daily high for Phoenix during July) for eight weeks, contained only fifty (50) percent of the original amount of APM. A cola beverage held under the same conditions contained only forty (40) percent of the original APM amount. And beverages exposed to higher temperatures degrade even more rapidly. And, of course, because of the temperature elevation ratios, product temperatures could easily be much higher during actual conditions than the stable temperatures used in the Searle laboratory studies.

Thus, it is known that APM will degrade rapidly at high temperatures, including temperatures to which soft drinks are known to be exposed intermittently during the summer. What is now known, although the FDC Act requires the proponent of use to demonstrate it, is what effects of degradation occur by virtue of exposure to these temperatures. More specifically, to demonstrate that APM is safe for use in soft drinks, the petitioner must reasonably identify what degradation products are formed under those conditions. Ultimately, of course, the safety of the major degradation products must be determined. Under the FDC Act, the data needed to make that determination—reliable and competent data—must be provided by the petitioner.

Objection Two: Searle has not demonstrated that APM use in soft drinks will not adulterate the beverages under Section 402(a)(3) of the FDC Act.

SUMMARY OF BASIS FOR OBJECTION

As discussed above, it is well established that the petitioner for issuance of a regulation authorizing the use of a food additive bears the burden of proving, through reliable and competent data, each element of the criteria set forth in section 409 of the FDC Act, 21 U.S.C. § 348, for issuance of a food additive regulation. The present record does not contain data which demonstrate that the use of APM in soft drinks will not result in the adulteration of the beverages under section 402(a)(3) of the FDC Act, 21 U.S.C. § 342(a)(3), which provides that a food is adulterated if it contains, in whole or in part, ". . . a decomposed substance or if it is otherwise unfit for food." Indeed, the present record strongly suggests that the rapid degradation of APM in soft drinks and the consequent loss of sweetness may well result, under certain actual time and temperature conditions, in products which would be adulterated under section 402. Without data which demonstrate that APM-sweetened beverages will not be adulterated under section 402(a)(3), Searle has not met its burden of proof under section 409(c)(3)(B) of the FDC Act, 21 U.S.C. § 348(c)(3)(B).

FACTUAL BASIS FOR OBJECTION TWO

The marked and rapid decomposition of APM in soft drinks under temperatures known to prevail is apparent from data in the present record and discussed above in these objections. Those data show that it is reasonable to expect APM to decompose in soft drinks sufficiently rapidly under current handling and distribution procedures

[9] The use of exaggerated, but realistic, test conditions is a routine facet of testing to establish the safety of food additives. For example, pursuant to FDA guidelines, extraction testing to detect and quantify migrants from packaging materials is required to be conducted under temperatures and for time periods which are known to exceed actual conditions of use.

[10] Similar, but equally limited studies were conducted using carbonated beverage bases (syrups).

[11] In the preamble to the regulation authorizing APM use in soft drinks, FDA itself acknowledged this phenomenon. "At temperatures above 30 C (86 F) the stability drops off markedly." 48 *Fed Reg.* at 31377. As shown below, soft drinks are frequently exposed to temperatures well in excess of 30 C (86 F).

[12] Searle FAP at 14, Fig. 3

[13] High summer temperatures are by no means limited to the southern states. During the period July 10 to July 24, 1983, for example, St. Louis, Missouri experienced 14 consecutive days of temperatures over 90°F, and 10 days of temperatures of 95°F or greater. During the same period, Louisville, Kentucky experienced similar temperatures.

[14] Study cite. A full description of this study is contained in Appendix ——.

[15] Full sun exposure occurs, for example, when a service station runs a promotion in which cases of the beverages are stacked in front of the station in full view of passing motorists and therefore often in direct sunlight.

[16] This temperature exceeds by 11°C (20°F) the highest temperature used in Searle's stability studies. In those studies, after less than four weeks, beverages stored at 55 C (131 F) contained less than twenty (20) percent of the original amount of APM. (Searle FAP at ??)

to adversely affect product quality and taste.[1]

It is well-established under section 402(a)(3), that a food which contains a decomposed substance (i.e., the decomposition products of APM which, Searle's data show, can readily exceed the quantity of APM itself in a short time)—especially where the decomposition has adversely affected product quality or made the product unpalatable—is adulterated and subject to seizure. (cites). It is quite clear, for example, that FDA would consider beverages which had lost substantial sweetness because of APM decomposition and which were therefore not palatable, to be adulterated under section 402(a)(3). The record is devoid, however, of evidence which demonstrate that APM used to sweeten soft drinks will not, under reasonably anticipated conditions of use, in fact cause the products to be adulterated. Without such evidence Searle has not met the burden imposed under section 409(c)(3)(B).

[This objection will be expanded.]

Objection three: Searle has not demonstrated that APM is functional for use in soft drinks under temperature conditions likely to prevail in the United States.

SUMMARY OF BASIS FOR OBJECTION

In addition to data intended to assess the stability of APM in soft drinks, Searle's petition for use of APM in soft drinks contains data intended to show that APM is functional in the beverages, i.e., that it achieves and retains the intended technical effect (sweetening) under the conditions of use reasonably anticipated to occur. Searle has not demonstrated that APM is functional in soft drinks because its data show a significant loss of sweetness at temperatures to which soft drinks are known to be exposed and within the range of time periods between bottling and projected consumption. The functionality of an additive cannot be considered to have been demonstrated if significant loss of its intended technical effect (because of temperature and pH dependent degradation) may occur under reasonably anticipated conditions of handling, storage and use.

FACTUAL BASIS FOR OBJECTION THREE

To evaluate the functionality of APM, Searle conducted "sensory evaluation" tests which used consumer taste panels to assess "perceived sweetness" (cola, beverages only) and "overall liking" (or "acceptance") (all flavors) over time periods up to 52 weeks and at three temperatures: 5°C (41°F), 20°C (68 F) and 30°C (86°F). Beverages sweetened with APM only (5, 20 and 30°C) and APM with saccharin (20°C) were tested; beverages sweetened with sucrose (——°C) and saccharin (——°C) were used as references. The beverages were rated at different time periods by the panelists.[2]

Although no temperature used in Searle's sensory evaluation tests approached the actual product temperatures which soft drinks will reach (see section —— above), significant loss of sweetening and overall liking occurred for beverages sweetened with APM only within extraordinarily short time periods. For example, APM-sweetened cola beverages stored at 30°C (86°F) received an overall liking score of less than 20 on a 0-100 scale after only 20 weeks (after 20 weeks the product was apparently unpalatable, since Searle did not present sensory evaluation data beyond this time). For an orange beverage, overall likeness after 20 weeks at 30°C (86°F) approached 5 (on a nine point hedonic scale), the "neither like nor dislike" or mean rating. Again, sensory evaluations were apparently not conducted beyond 20 weeks.

Searle's characterization of the results of the sensory evaluation tests avoids the clear implication of those tests: That APM has not been shown to retain sufficient sweetness at temperatures which are known to occur for APM-sweetened beverages to retain an acceptable "overall liking" rating. Instead, Searle emphasizes an interesting, but legally irrelevant finding: That APM sweetened beverages tested after holding at relatively low temperatures were preferred to beverages sweetened with alternative sweeteners. This characterization misses the statutory purpose for which the studies were undertaken, that is, to demonstrate that APM is a functional sweetener in soft drinks.

Of particular importance is the fact that Searle's sensory evaluation tests do not explore the effects on either sweetness or overall likness of APM-sweetened beverages exposed, either consistently or intermittently, to the higher temperatures which prevail in much of the United States. What is the effect on these two measures, for example, of product temperatures of 100 to 120°F? Is the degradation greatly accelerated and the overall liking therefore diminished in even shorter time periods? Will APM-sweetened beverages stored in warehouses and carried on open route trucks or stored in warehouses and displayed in open air service station promotions in the southern states be acceptable when the consumer attempts to consume them several weeks later? Is APM a functional sweetner for soft drinks if APM-sweetened beverages in certain parts of the country would, during the summer months, have to be treated as if they were perishable commodities?[3]

[To be expanded with age distribution data.]

Ojection No. Four: G.D. Searle and Company Has Not Demonstrated To A Reasonable Certainty That The Use of Aspartame In Soft Drinks, Without Quantitative Limitation, Will Not Adversely Affect Human Health As A Result Of The Changes Such Use Is Likely To Cause In Brain Chemistry And Function Under Certain Reasonably Anticipated Conditions Of Use.

SUMMARY OF BASIS FOR OBJECTION

In its July 8 Federal Register notice, FDA acknowledged receiving a comment expressing concern about the effect on plasma and brain phenylalanine (PHE) and tyrosine (TYR) levels when aspartame is fed in combination with a carbohydrate. 48 Fed. Reg. at 31379. The comment included data demonstrating that in both rats and humans the feeding of a carbohydrate with aspartame significantly enhances aspartame's positive effect on the ratio of PHE and TYR to other large neutral amino acids (LNAA) in the blood. The data submitted with the comment also demonstrate that brain PHE and TYR levels in the rat are significantly increased by the aspartame/carbohydrate combination.

The concern of the commenter, Dr. Richard J. Wurtman, Professor of Neuroendocrine Regulation at the Massachusetts Institute of Technology, was that increased brain levels of PHE and TYR are likely to affect the synthesis of certain neurotransmitters—substances vital to the regulation of brain function—and that changes in the levels of neurotransmitters could in turn cause adverse physiological effects (by, for example, modifying the function of the autonomic nervous system) and/or behavioral effects.

FDA responded to Dr. Wurtman's comments by stating that it ". . . believes that the comment's conclusion regarding potential phenylalanine induced changes in neurotransmitter function appear to be unwarranted extrapolations . . ." (48 Fed. Reg. at 31379; emphasis added) and by concluding that ". . . the data supplied with this comment do not provide support for its hypothesis that the ingestion of aspartame and carbohydrate will alter the brain levels of neurotransmitters and thereby produce behavioral modifications." 48 Fed. Reg. at 31380. FDA cited as support for its conclusion several studies submitted by Searle; FDA did not discuss, however, much of the data submitted by Dr. Wurtman (including those demonstrating significantly elevated brain levels of PHE and TYR), and it apparently overlooked the significance of aspartame's demonstrated blocking effect on glucose-induced elevation of brain serotonin levels.

In light of the allocation of the burden of proof and the nature of the safety standard in food additive proceedings (discussed above), FDA's handling of Dr. Wurtman's concerns was unusual. The tone of the July 8 notice suggested that the burden was on Dr. Wurtman to demonstrate that aspartame is harmful and that, absent affirmative demonstration of harm (which obviously is lacking at this point), aspartame must be approved. To the contrary, however, the burden is on Searle to prove to a reasonable certainty that no harm to human health will result from aspartame. Thus, the question for FDA in evaluating Dr. Wurtman's concern is whether, in the minds of competent scientists, the questions posed by Dr. Wurtman and his data are sufficiently significant from a safety standpoint that they should be more thoroughly addressed by Searle in order to provide the statutorily required "reasonable certainty" that no harm will result from aspartame's use.

We object to the approval of aspartame for unrestricted use in soft drinks (which could be as high as 550 mg/liter, or higher) on the ground that Searle has not made the required showing. This objection is supported by the following points, which are discussed further below and supported by the accompanying affidavits: (1) available evidence demonstrates that the consumption of aspartame/carbohydrate combinations by rats in amounts comparable to those likely to be encountered by humans under certain

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[1] FDA acknowledges this distinct possibility when it states its "belief" that changes in these procedures will avoid the problem. Section 409(c)(3)(B) does not contemplate that a "belief" in unspecified, but fundamental, changes in industry practice are necessary to assure that widespread use of a food additive will not adulterate the food.

[2] For stating rating periods.

[3] In the preamble to the APM regulation, FDA dismissed summarily the concern about the functionality of APM in soft drinks at temperatures above 30°C (86°F): "The agency believes, however, that storage at these times and temperatures can be avoided by attention to handling and distribution." (48 *Fed. Reg.* at 31377). This summary resolution of the functionality issued is inconsistent with the FDC Act for two reasons. First, it is based on the agency's "belief" and not on any objective evidence. The Act requires the agency to resolve material issues based on facts, not on beliefs. Moreover, the facts—actual temperature conditions to which the beverages are exposed and actual beverage temperatures—suggest that degradation and consequent loss of sweetness and overall liking (and hence functionality) may occur within even shorter periods than the agency appeared to find acceptable.

Second, the purported resolution of the functionality issue by assuming that significant loss of sweetness "can be avoided by attention to handling and distribution" is an assumption unsupported by any evidence in the present record (none is cited by the agency). In all likelihood, the agency's "resolution" is entirely impracticable. To assume that fundamental changes in handling and distribution will occur to avoid an acknowledged functionality problem turns the FDC Act on its head.

reasonable anticipated conditions of use elevates plasma ratios of PHE and TYR significantly and brain PHE and TYR levels by factors of 3.0 and 3.5, respectively; (2) available evidence from human studies demonstrates that consumption of aspartame/carbohydrate combinations in amounts likely to be encountered under certain reasonable anticipated conditions of use elevates human plasma levels of PHE significantly beyond the normal range; (3) there are sound scientific reasons to believe that human brain levels of PHE and TYR will respond to aspartame consumption in a manner similar to rats; (4) there are sound scientific reasons to believe that increased brain levels of PHE and TYR could affect the synthesis of neurotransmitters and in turn various physiological functions and/or behavior; for example, TYR is a known precursor of the catecholamine neurotransmitters, and tryosine levels have been shown to affect several bodily functions controlled by the autonomic nervous system (including regulation of blood pressure); and (5) the demonstrated ability of aspartame to inhibit the glucose-induced release of serotonin has the potential to affect important serotonin-mediated behaviors, such as satiety, food choice, and sleep.

Despite the potential effects of aspartame/carbohydrate combinations, the present record is devoid of readily obtainable evidence that could resolve whether the effects are in fact likely to occur. As will be demonstrated, the data cited by FDA in its July 8 notice are not sufficient to resolve the issue. It would be possible, however, to perform within approximately six months studies in rats that would resolve conclusively whether levels of aspartame and carbohydrate corresponding to those likely to be consumed by humans would affect the synthesis of neurotransmitters and in turn cause detectible physiological and behavioral effects. It also would be possible to perform additional short-term studies in humans to determine whether aspartame/carbohydrate combinations have observable effects on physiological parameters (such as blood pressure) or behavior.

For these reasons, Searle has not met its burden of demonstrating to a reasonable certainty that the unlimited use of aspartame, especially in combination with carbohydrates, will not adversely affect human health. The questions posed by Dr. Wurtman are significant because of the seriousness of the potential effects (e.g., changes in blood pressure) and because of aspartame's anticipated widespread use—use that includes consumption by potentially vulnerable sub-groups, such as children, pregnant women, and hypertensives. Dr. Wurtman's concerns are shared by other distinguished scientists expert in this field (affidavits attached). It is Searle's legal burden to submit data sufficient to resolve the concerns.

FACTUAL INFORMATION SUPPORTING OBJECTION FOUR

1. FDA has underestimated the amount of aspartame that can be consumed through its use in soft drinks because the agency has focused on adult users (assumed to average 60 kilograms in weight). FDA relied upon an intake value of 34 mg/kg/day in assessing the possible risks of aspartame, describing that level as the "... highest obtained from any estimate of potential consumption and exceed[ing] the 99th percentile consumption (25 mg/kg) for all age groups ..." 48 Fed. Reg. at 31377. For a 30 kg child, however, it would not be unusual for that level to be achieved or, in terms of the effect on plasma PHE levels, even exceeded. For example, if a 30 kg child consumed on a warm day after exercise approximately two-thirds of a two-liter bottle of soft drink sweetened solely with aspartame, that child would be consuming approximately 700 mg of aspartame, or approximately 23 mg/kg. This alone roughly equals what FDA considered the 99th percentile consumption level. If during the day this child consumed other aspartame-sweetened products, the exposure level could quickly approximately FDA's so called "loading dose" of 34 mg/kg. 48 Fed. Reg. at 31377. In addition, however, data derived from rats and humans demonstrate that concurrent consumption of a modest amount of carbohydrate (approximately 3 grams per kg, or, for a 30 kg child, perhaps several cookies) approximately doubles the effect of the aspartame on the ratio of plasma PHE to other large neutral amino acids (LNAA) (Wurtman affidavit). Thus, in terms of effect on the PHE/LNAA ratio in the blood, the above-described concurrent consumption of aspartame and a carbohydrate is equivalent to an aspartame dose of as much as 50 to 60 mg/kg.

2. Aspartame has been tested in rats to determine the effect of aspartame and aspartame/carbohydrate combinations on the plasma ratios and brain levels of various amino acids (Wurtman affidavit). In rats fed 200 mg/kg aspartame, the plasma PHE/LNAA ratio increased to 0.185 from 0.110 in the controls, and the brain PHE level increased from 52 n-moles/g in the controls to 110 in the treated animals. When the same amount of aspartame was fed with 8 g/kg glucose, however, the plasma PHE/LNAA ratio increased sharply again to 0.240, while the brain PHE level increased to 143 n-moles/g. In addition, there was a 3.5-fold increase in brain TYR levels.

3. Aspartame and aspartame/carbohydrate combinations have also been tested in humans by Searle and Dr. Wurtman (cite to Searle petition and Wurtman affidavit). An aspartame dose of 34 mg/kg significantly elevated the plasma PHE/LNAA ratio, an effect that is almost doubled by the addition of 30 g of carbohydrate (equivalent to 4 or 5 cookies).

4. It is not possible to measure in vivo human brain levels of amino acids resulting from consumption of aspartame or subsequent effects on neurotransmitter synthesis. There are sound theoretical reasons, however, for considering the rat to be an appropriate model for assessing possible human effects (Wurtman affidavit). Moreover, there is empirical evidence to support the use of the rat as a model for evaluating possible effects of aspartame on human brain chemistry (Wurtman affidavit).

5. There is scientific evidence suggesting that increases in brain PHE and TYR levels on the order seen in the rat studies can effect synthesis of neurotransmitters, which themselves can effect important physiological functions and potentially behavior. [Wurtman affidavit should catalogue this evidence.] Readily available tests could determine whether aspartame has such neurotransmitter effects in rats or effects the rat's physiological functions or behavior. [Wurtman affidavit should describe tests.]

6. Aspartame has been demonstrated to inhibit the carbohydrate-induced-synthesis of the neurotransmitter serotonin (Wurtman affidavit). Serotonin blunts the sensation of craving carbohydrates and thus is part of the body's feedback system that helps limit consumption of carbohydrate to appropriate levels. Its inhibition by aspartame could lead to the anomalous result of a diet product causing increased consumption of carbohydrates.

EXHIBIT 2

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES,
May 13, 1981.

To: The Commissioner through the Acting Deputy Commissioner.

From: Acting Associate Commissioner for Health Affairs.

Subject: Aspartame.

Attached is an agenda for Thursday's 3:00 p.m. meeting on aspartame. We plan to present a scientific briefing on the safety issues and, therefore, the staff scientists involved will be present also. I have asked Joe Levitt, Office of General Counsel, as team leader, to coordinate the discussion. We also need to discuss our timetable for issuance of a final decision.

The first and primary agenda item relates to the brain tumor issue. This was the point on which the Public Board of Inquiry concluded that safety had not been shown. A first draft "final decision" on this issue is attached.

As mentioned in our last meeting, the team is not unanimous in its recommendations. The draft disagrees with the Board and concludes that safety has been shown on this issue. Those not in agreement, principally the statisticians, have prepared their views separately (Tabs A, B, and C) so as to give you a balanced picture.[1]

The major issue discussed at the hearing was the background rate for spontaneous brain tumors in the specific strain of rat used by Searle. The team is in the general agreement that the Board adopted too low a figure. This issue is discussed in detail in Section B of the attached draft.

The major issues of disagreement among the team members are as follows:

1. *Power (or Sensitivity) of the Studies:*

Searle has complied with the old Bureau of Foods standard of 40 animals per sex per group, applicable in the early 1970's when the studies were conducted. The current standard is 50 animals, although studies with 40 per group are considered "very useful" (Bureau of Foods testimony) for "cyclic review" purposes. Cyclic review is the process by which the Bureau of Foods re-evaluates substances on the GRAS list, usually based on older studies. The threshold question, then, is whether 40 animals per group are sufficient for the aspartame studies.

Assuming that 40 animals will be deemed sufficient in this case, the team is in agreement that if the data, raise a suspicion of carcinogenicity, additional studies of considerably larger power will be necessary. The disagreement here is whether the data raise that suspicion.

The Board did not need to reach this issue, but at one point noted that one study (E-70) should have included more animals.

2. *Dose Response in Females, Study E-33/34:*

In the major rat study (E-33/34) a statistically significant dose response was found for the females using the Cox (P=.04) and Breslow (P=.02) tests. Both take into account time of death of the test animals, and the Breslow test gives extra weight to early occurring tumors. However, the significance of these findings is heavily dependent on a me-

[1] As additional background material, enclosed is a summary of the legal and scientific framework for approval of a food additive petition (Tab D), and summaries of the evidence in the Cyclamate and Red No. 2 decisions, for comparison purposes (Tab E). The Board's Decision, the Cyclamate Decision, and a historical chronology on aspartame were attached to my previous memorandum dated April 24, 1981.

dulloblastoma found in a high dose female at 12 weeks, which the Bureau and Searle argue was not aspartame related. By deleting the medulloblastoma, the statistical results change dramatically (P=.15 for the Cox test and P=.13 for the Breslow test). The biological scientists agree with Searle and the Bureau that this tumor may not have been caused by aspartame, and, therefore do not consider these findings to be of biological significance. The statisticians disagree. Both positions are detailed in the attached materials.

The Board also discussed dose response in this study, but in a slightly different fashion.

3. *Types of Statistical Analyses Used:*

Searle used certain statistical tests to analyze the data, and the Bureau of Foods different tests. Dr. Dubey has applied additional tests, not employed by either party, which he believes give a more appropriate interpretation of the data (see Tab B). For example, one test called the significant risk analysis is especially important to Dr. Dubey's position. We will, therefore, need to decide which statistical tests are to be employed. While deviating from the tests used by the parties creates certain legal and policy problems, these are not unresolvable. The Board did not discuss any of these statistical techniques.

4. *Conduct of the Studies:*

The conduct of all three rat studies has been criticized by Dr. Olney. Some of the staff scientists believe the studies were adequately conducted, while others tend to agree with Dr. Olney that one or more of the studies was severely flawed. Again, the different positions are documented.[1]

I anticipate that discussion of these issues will take up most of Thursday's meeting.

The second agenda item is a status report on the other safety issues raised, involving increased levels of phenylalanine and aspartic acid consumption. In general, we anticipate agreeing with the Board that safety has been shown on these issues, although parts of the Board's decision will need to be corrected. Materials on these issues are contained at Tabs G and H.

The final agenda item is the status conference scheduled in federal court on Wednesday, May 15, when the Agency will be called upon to project a date when the final aspartame decision will be made. We will be prepared to discuss this timetable with you at Thursday's meeting.

ALLAN B. DUNCAN
(For Stuart L. Nightingale, M.D.).

AGENDA

I. Brain Tumor Issue:
A. General Overview—Mr. Levitt.
B. Background Spontaneous Rate—Dr. Jackson; Dr. Cameron.
C. Review of Aspartame Studies:
1. Power—Dr. Condon.
2. Dose Response—Study E-33/34—Dr. Condor.
3. Statistical Analyses—Dr. Dubey.
4. Conduct of the Studies—Dr. Dubey.
II. Brain Damage Issues:
A. Phenylalanine—Dr. Gryder.
B. Aspartic Acid-Glutamic Acid—Dr. Rosloff.
III. Timetable for Final Decision.

APPENDICES

TAB A—Comments on Brain Tumor Issue—Dr. Condon.
TAB B—Comments on Brain Tumor Issue—Dr. Dubey.
TAB C—Comments on Brain Tumor Issue—Dr. Park.
TAB D—Legal and Scientific Framework.
TAB E—Cyclamate Evidence; Red No. 2 Evidence.
TAB F—Mr. Turner's Appeal.
TAB G—Brain Damage (Phenylalamine).
TAB H—Focal Brain Lesions (Aspartic Acid).

Mr. METZENBAUM. Mr. President, I now send my amendment to the desk and ask for its immediate consideration.

The PRESIDING OFFICER. The Senator is reminded that the pending business is the committee amendment which must be disposed of before the amendment of the Senator from Ohio is considered.

Mr. HATCH. Mr. President, if the Senator will withhold, I will get the committee amendment passed, and then we can take up his amendment.

Mr. President, the committee adopted an amendment changing the term of the bill from 3 years to 2. Therefore, I move the committee amendment be adopted.

The PRESIDING OFFICER. If there is no further debate on the committee amendment, the question is on agreeing to the committee amendment.

The committee amendment was agreed to.

Mr. HATCH. Mr. President, I move to reconsider the vote by which the committee amendment was agreed to.

Mr. METZENBAUM. I move to lay that motion on the table.

The motion to lay on the table was agreed to.

Mr. THURMOND. Mr. President, I rise in support of S. 484, the Saccharin Study and Labeling Act and urge its passage without further amendment. This bill would extend for an additional period of 2 years the original saccharin moratorium that was enacted in 1978 and later extended.

This extension would prohibit the Secretary of Health and Human Services from restricting the sale or distribution of saccharin solely on the basis of research available to the Secretary on the date of the original enactment of this moratorium. The original moratorium legislation provided for continued research as to any causal relationship between saccharin consumption and human cancer. This bill would maintain this requirement of continued research.

Dr. Frank Young, Commissioner of the Food and Drug Administration, in his testimony last month before the Labor and Human Resources Committee stated that a link between saccharin consumption and human cancer has not yet been proven, despite years of intensive research. The research to date indicates that saccharin, when consumed in high doses, may cause bladder cancer in rats, but not in mice. Since there has never been definitive scientific proof that saccharin causes cancer in humans, further research efforts as outlined by officials of the Food and Drug Administration should continue. In the meantime, the millions of Americans, including diabetics, who rely on saccharin as a sugar substitute should not be deprived of its availability.

The amendment which I understand the Senator from Ohio, Mr. METZENBAUM, will propose would require the manufacturers of diet soft drinks to include on their label how much aspartame each serving contains. Aspartame, or its commercial name "NutraSweet," is a chemical combination of two naturally occurring amino acids found in foods that we eat daily. In 1980, the FDA approved aspartame for certain purposes after subjecting it to years of study. There has never been any evidence that aspartame causes cancer. When it was approved, the Commissioner of the FDA at the time, Dr. Arthur Hayes, noted:

> Few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety".

Unfortunately, aspartame cannot be used as a sweetener in cooking because it loses its sweetness when heated. Therefore, it cannot be a complete saccharin substitute.

Currently, the Food and Drug Administration has sufficient statutory authority to require the labeling suggested by my distinguished colleague from Ohio. If the FDA, based on their continued research and expertise, determines that such label requirements are necessary, then Congress should defer to the Agency's judgment. Otherwise, mandating the quantitative labeling of a product which has proven to be safe would be one more unnecessary Federal burden placed on the private sector.

Mr. GRASSLEY. Mr. President, I am a cosponsor of this bill, S. 484, the Saccharin Study and Labeling Act, and I intend to vote for the bill as it was reported from the Committee on Labor and Human Resources of which I am a member.

With respect to the continuation of the moratorium on the ban on saccharin, which this bill provides, it is clear that this moratorium should be continued. As is clear from the testimony the committee received at our hearing on April 2, 1985, the jury is still out on saccharin. No clear verdict emerges from the considerable research effort which has been directed to finding out whether this sweetener does indeed cause cancer in humans when consumed in normal amounts.

Although it is clear that we should satisfy ourselves that there is no health hazard from use of saccharin we also do not want to rush forward to ban this product on the basis of inconclusive evidence. We have had enough experience with hasty judgments, based on flimsy evidence, about products on which many people depend, both consumers and producers.

[1] The Board refused to hear evidence on the conduct of the studies. For that reason, Mr. Turner has appealed for a new hearing. That issue is addressed in Tab F.

It is appropriate, therefore, that we extend this moratorium until the Food and Drug Administration can demonstrate conclusively that this product causes cancer. In any case, the Food and Drug Administration does have the authority to withdraw saccharin from the market at any time if research findings indicate conclusively that it is dangerous to human health.

With respect to aspartame labeling, which is also at issue here today, it seems to me to be premature to require this since the burden of testimony at the April 2 hearing was that aspartame is safe at normal consumption levels. Dr. Lewis Stegnick, an expert from the University of Iowa, testified on April 2 that:

In conclusion, based on our research, I concur with the findings of the FDA and regulatory authorities around the world that aspartame is safe at expected levels of consumption.

Therefore, I will support the bill as it was reported from the committee and will not support the amendment offered here today with respect to aspartame labeling.

Mr. NUNN. Mr. President, today we are considering the continued availability of saccharin, one of the two nonnutritive sweeteners on the market today. Saccharin has undergone more scrutiny and scientific research than any other substance in the food supply. Since 1977, when the FDA proposed to ban saccharin, the Congress intervened on three occasions and provided a moratorium on such action by the FDA.

Saccharin is a sweetener that has been used worldwide for more than 80 years. Recently, many significant new studies have expanded our understanding of the safety issues surrounding saccharin and its appropriate use as a food additive. Last year the largest study ever conducted on saccharin was completed. The expert panel which evaluated the scientific findings along with other current studies concluded that "the present exposure of humans to saccharin through its use as a food additive presents an insignificant cancer risk." It is my understanding that the many studies on human groups consuming large quantities of saccharin, such as diabetics, have never shown a correlation between human cancer and saccharin consumption. The only problems to have ever surfaced occurred when male rats were force fed the equivalent of several hundred cans of diet soda containing saccharin per day.

In addition to considering the absence of a relationship between saccharin consumption and human cancer, we must also consider the tremendous benefit that saccharin affords diabetics and others who for health reasons should not consume sugar. Diabetes is the No. 3 cause of death by disease in the United States and the No. 1 cause of new cases of blindness in adults over 20. People with diabetes are at high risk from heart disease, stroke, kidney failure, and severe nerve damage.

Unlike previous congressional consideration of the saccharin situation, we have a new sweetener on the market now, named aspartame. Consumer acceptance of this product in diet beverages and table top sweetener use has been rapid. Aspartame, however, is not a substitute for saccharin as it cannot be used in cooking, or baking, or in heat processed foods. Also, saccharin is the only approved low-calorie sweetener for many cosmetic and pharmaceutical products.

Americans should have a variety of sweeteners available to them. The Congress needs to extend the moratorium on saccharin and proceed with a comprehensive evaluation of food safety, labeling, and all other scientific aspects of the American food supply. I hope you will join me in voting for this legislation which would extend the moratorium on saccharin.

Mrs. HAWKINS. Mr. President, I am a cosponsor of S. 484, the Saccharin Study and Labeling Act, and I plan to vote for its passage today. I also plan to vote against the amendment offered by the distinguished Senator from Ohio, Senator METZENBAUM, regarding quantitative labeling of aspartame. Since I am a strong supporter of the consumer's right to know about the products they are consuming and an original cosponsor, with Senator METZENBAUM of the Dietary Information Act of 1985, I want to explain my reasoning for voting against this amendment.

Mr. President, I believe that quantitative labeling of products and additives is extremely useful to consumers with certain dietary restrictions. In the case of sodium and fat content, the correct labeling of products may make a major difference in the health of an individual who suffers from high blood pressure or a heart condition. But this quantitative labeling is useful because countless studies and reports have documented the link between sodium and fat intake and certain cardiovascular conditions. Quantitative labeling of aspartame or NutraSweet would not be useful because so far, there has been no medical or scientific studies demonstrating a health risk associated with consumption of aspartame in any quantity. Therefore, what difference will it make to a health conscious consumer whether there is 50 milligrams of NutraSweet or 500 milligrams of NutraSweet in the product?

I realize that some scientists and organizations have expressed concern about the validity of the testing procedures used to gain FDA approval of aspartame. While I do not feel that they have presented enough evidence to justify removing the product from the market pending these tests, I do agree that the concerns that they have raised regarding the long-term effects on the health of children justifies requiring additional tests to be done on this product. The Senate Labor and Human Resources Committee report accompaning S. 484 directs the Food and Drug Administration to carry out further testing of that product. If the additional testing of aspartame indicates a health risk associated with consumption of aspartame in certain quantities, then my views regarding quantitative labeling of aspartame would change. But until medical and scientific evidence indicates such a health risk, then I believe quantitative labeling of aspartame would be of little of no value to the consumer.

Mr. D'AMATO. Mr. President, I rise today on behalf of S. 484, introduced by my good friend, the junior Senator from Utah and the distinguished chairman of the Labor and Human Resources Committee. I commend the Senator from Utah for his introduction of this legislation to extend for 2 years the moratorium on the ban of saccharin.

As we all are aware, Americans have come to rely on low-calorie sweeteners to control their diets. Of the nearly 70 million people who use sugar substitutes, about 50 million depend on saccharin. We should not delay or impede the access of saccharin to these people, a good portion of whom are diabetic.

The main reasons for this extension are simple. There is no evidence that the use of saccharin has an adverse effect on our Nation's health. Saccharin is one of the most tested food substances. Because of its 80 years of use without being linked to cancer, it has passed the all important test of time. Twenty human studies on saccharin support its safety. In fact, the absence of saccharin would be harmful to millions who must avoid sugar to avoid medical problems associated with being diabetic or overweight. Test after test has shown that saccharin does not cause cancer in animals other than rats or at sites other than the bladder. I am not aware of any study which shows an association between saccharin intake and bladder cancer in humans. One study indicated that saccharin caused bladder tumors in rats when applied in 3 percent doses. This would equal 750 cans of diet soda consumed on a daily bases for a human lifetime.

Another important reason to keep saccharin on the market is lack of another complete sugar substitute. Although aspartame is used as the sugar substitute, its use is not as universal as saccharin's. Unlike saccharin, aspartame cannot be used in most cooking or baking because of sweetener loss. A gradual sweetening loss also occurs when aspartame is used in liquids. Although the FDA supports its use, many scientists continue to fear the health effects of aspartame.

Cyclamates, which are being reconsidered to be let back on the market, are not a complete sugar substitute either. Its sweetener intensity is too low, and for many instances would re-

quire its use in combination with other substitute sweeteners. Also, its effects are still suspect. Some experts fear that it may cause chromosome breakage and could cause testicle atrophy. Even if the ban on cyclamates was reversed, the product could not be available until late this year at the earliest.

The ideal low-calorie sweetener which could meet the growing consumer demand for a greater variety of reduced calorie products does not exist. Neither saccharin, aspartame, nor any other sweetener is perfect on all accounts. The answer for meeting this demand seems to be a multiplicity of sweeteners, each allowed to find its most effective role in the marketplace. The net result of a variety of sweeteners will be better-tasting products that have adequate shelf life, extended safety margins, lower production costs for industry, and more product choices for the consumer.

Because of the use of other sweeteners is limited, it is only reasonable to continue to allow saccharin on the market. Saccharin is the least expensive sugar substitute available. It is important to millions of people dependent on saccharin that its availability not be disrupted.

The public outcry in 1977 when the FDA first decided to ban saccharin should not be forgotten. The use of saccharin was important to the public in 1977 and it continues to be important today.

The current moratorium ended last month. I support the continuation of studies on saccharin, but we must let the millions of Americans who depend on saccharin for their restricted diets know that they will continue to be able to use saccharin until at least May of 1987 or until another all purpose sugar substitute is found. I support passage of S. 484.

Thank you, Mr. President.

AMENDMENT NO. 60

(Purpose: To provide that any soft drink which contains aspartame shall be considered to be misbranded unless the label or labeling of such product states the total number of milligrams of aspartame contained in such serving of such soft drink)

The PRESIDING OFFICER. The clerk will report the amendment of the Senator from Ohio.

The legislative clerk read as follows:

The Senator from Ohio [Mr. METZENBAUM] proposes an amendment numbered 60.

Mr. METZENBAUM. Mr. President, I ask unanimous consent that further reading of the amendment be dispensed with.

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

The amendment reads as follows:

At the end of the bill, add the following:

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) If it is a soft drink which contains aspartame, unless its label or labeling states the total number of milligrams of aspartame contained in each serving of such soft drink."

(b) The provisions of section 403(q) of the Federal Food, Drug, and Cosmetic Act (as amended by subsection (a) of this section) shall take effect no later than eighteen months after the date of enactment of this Act.

Mr. METZENBAUM. Mr. President, I wish to point out to my colleague from Utah, in case he missed it earlier, at one point we talked about there being a 6-month lag period for the soft drink companies to comply. We made that 18 months in the amendment.

Mr. President, I reserve the balance of my time.

Mr. HATCH. Mr. President, I must oppose the amendment by the Senator from Ohio for several reasons. First, this bill addresses saccharin. It is one sentence long and in its present form it is uncontroversial. If it passes the Senate "as is," it will be taken up immediately in the House, where favorable consideration is expected. At least that is what the House leadership has indicated to me. If it is amended to include aspartame labeling, the House leadership has informed us it will be derailed over there.

Now, I heard the distinguished Senator from Ohio and I was interested in his comments on that point. But, be that as it may, I still would have to oppose the amendment.

Second, this issue, which the Senator would have us believe is so simple, is actually complex and uncertain.

As an example, in his "Dear Colleague" addressed to this amendment, the Senator states that labeling is advised, among other reasons, because "a four-year-old weighing 30 pounds would hit that limit (the acceptable daily intake of aspartame) at three cans of diet soda." Yet FDA has furnished us with actual consumption data showing that a 2- to 5-year-old child at the 99th percentile of aspartame consumption ingested scarcely one-third of the acceptable daily intake, for the period July-September of 1984. Now I am not sure what these different statements imply, if indeed both are correct, but I do know that we are not well equipped to resolve them in this bill.

And this is my point: We have set up the Food and Drug Administration, and a careful set of procedures for the examination and resolution of these sorts of issues, for obtaining public comment, for obtaining outside scientific review, for the conduct of surveys and the weighing of implications. The Food and Drug Administration has the authority to require quantitative aspartame labeling right now. But it has never been petitioned to do so.

At FDA is where this issue should be resolved, not in this bill. FDA is the body that can reasonably determine whether there is an actual, as opposed to a speculative, need for quantity data. FDA is the body that can determine what usage patterns are, what the acceptable daily intake is, how it should be disclosed, and so forth. And I note here that the Senator rightly observes, "It will take some time to figure out," how to effectively put the ADI data on the can, if at all. He is not proposing that now, but what good does it do the consumer to know how much is in the can unless he knows what standard to measure it against?

No, we make a real mistake if we preempt FDA's consideration of the issue by adopting this amendment. And FDA has testified it would seriously and promptly address any request for quantitative labeling. That is the process we have set up and we should follow it. The hearing record is absolutely empty of any evidence of a substantiated public health crisis that would compel us to disregard the administrative process.

Finally, I would briefly like to make three other points which we dwell on at more length in the committee report:

First, because 99th percentile usage levels of aspartame remain well below the ADI, consumers do not need to monitor precisely their levels of the sweetner. For those who for one reason or another have a particular interest, such as researchers, content information is freely available from the manufacturers.

Second, the hypothesis that persons in the general population may be subject to a yet unidentified sensitivity to aspartame is so far unsupported by any published scientific data. The Centers for Disease Control studied some 600 consumer complaints in which aspartame was a potential factor, attempting to find some pattern. The conclusion: "We found, in summary, that no scientific constellation of symptoms clearly related to aspartame consumption was clearly identified."

While the committee report directs FDA to see that followup studies are done to try to determine if an unknown sensitivity exists, it remains only an unverified possibility and does not justify an act of Congress at this time.

Third, the hypothesis that aspartame may alter brain chemistry in such a way as to alter mood, cause headaches, et cetera, has been considered by FDA and numerous foreign agencies which have approved aspartame, and has not been confirmed in studies completed to date. Further studies are to begin soon, but the hypothesis is still speculative at this point and does not give us any reason to preempt FDA on the labeling issue.

Finally, let us recognize that this is not a label or no label question. Soft drink cans are currently required to declare in their labeling that they contain aspartame. Thus those who cannot metabolize aspartame's common amino acids, and those who desire not to consume it for whatever reason, are perfectly able to avoid it completely. This is the labeling step

that makes some sense, and we are already doing it.

I am as sympathetic to disclosure of important information to the consumer as anyone.

In fact, I think we will hold hearings on labeling in general, not on a product-by-product basis but in general, later in the year. I think that will please the distinguished Senator from Ohio.

But we could literally wrap a can or box in a long list of unpronounceable ingredients and quantities which would benefit no one.

It is for exactly this reason that FDA should be the forum where the quantity issue is initially judged, openly and with the benefit of continuing scientific input.

I would also like to address three points made by the Senator from Ohio in his remarks.

First, the Common Cause charges of irregularities in the approval of aspartame have been raised again today, as they have in several fora in the past. They have not held up under scrutiny.

The bottom line is this: the studies supporting aspartame's approval have been examined and reexamined. More than enough sound, valid studies exist to demonstrate aspartame's safety. FDA's approval procedure has also been thoroughly reviewed on a number of occasions, and the agency, both in briefings for my office and Senator METZENBAUM's and publicly, has given good, credible reasons why the decisions were made which are now being portrayed as unusual or improper. This substance has been under review for 10 years, and at our hearings on the bill no one suggested that it be taken off the market.

Further, the acceptable daily intake for a substance is based on an evaluation of studies in animals and when available, in humans as well. In the case of aspartame, both extensive animal testing and human clinical studies were used to calculate the ADI. The ADI is a conservative upper limit on the amount of a substance that can safely be consumed on a chronic or lifetime basis. It is not unusual nor unsafe for a person to consume more than the ADI on occasion.

The ADI for aspartame set by FDA and reevaluated and reaffirmed several times is 50 milligrams per kilogram of body weight. This ADI is based on a broad array of data, including clinical studies in which human volunteers received, with no ill effect, up to 200 mg./kg./day of aspartame, which is equivalent to approximately 5 pounds of sugar per day.

FDA estimated that if aspartame replaced all the sugar and saccharin in the diet, the 99th percentile of projected consumption of aspartame would be 34 mg./kg./day. Aspartame is judged to be safe because this estimate of maximum daily intake, 34 mg./kg./day, is substantially below the acceptable daily intake of 50 mg./kg./day. Indeed, the actual consumption figures themselves are even lower.

Finally, I would like to make a couple of comments concerning this draft National Soft Drink Association document. The Senator continues to make a mountain out of this molehill. The draft was placed in context both in the hearing and in the markup on this bill. Far from being a source of suspicion about either the safety of aspartame or the good faith motives of the association, it is instead a confirmation of both.

The soft drink manufacturers have had experience with having a sweetener in wide use pulled from the market, with all the fear, adverse publicity, and expense such an event generates, the cyclamate case in the late sixties.

It was also clear to them that if aspartame were approved in soft drinks, public demand would quickly lead to its widespread use in the industry.

Thus, from a basic concern for the safety of their customers, and to avoid the expense and mistrust generated by a later FDA mandated withdrawal, the industry had every reason to critically scrutinize this new sweetener and to satisfy itself there were no weaknesses in its record. This it did.

As an important aid in its examination of both the pros and cons of aspartame licensing in soft drinks, the National Soft Drink Association commissioned from an outside law firm a memo focusing on possible objections to licensing. This memo, because of the shortness of time allowed for comment on the licensing, was cast as a formal objection on the part of NSDA.

The association consciously investigated each of the points in the document and satisfied itself that FDA and Searle had good and valid answers to them before supporting the licensing of aspartame.

The NSDA Board of Directors never adopted these positions and the document was never filed. It remained simply an aid to discussion and analysis.

It's no different from memos which any of our staffs might submit to us as an option, options we find without merit and do not act on. Saying this draft document shows NSDA's secret intent is like obtaining a copy of one of these rejected internal Senate staff memos and claiming it represents the Members' real thoughts on the issue.

In conclusion I want to make clear just what we are being asked to do in this amendment. We are asked to require the labeling of the quantity of aspartame present—and only aspartame—because it might cause side effects through some as-yet-unknown and unidentified sensitivity. Let me quote the testimony of Dr. Wurtman, the originator of this suggestion, to demonstrate how speculative it is:

> If aspartame does produce side-effects involving the brain, and if these side-effects result from the sweetner's phenylalanine content, then their production almost certainly requires that large amounts of aspartame—probably several grams—be consumed.

Thus it is claimed that consumers would need to know how much their intake is on a can-by-can basis.

Dr. Wurtman elsewhere in his testimony forthrightly admits that there is "an absence of positive evidence that aspartame produces deleterious effects." Thus what we have here is one "if" stacked on another "if". It reminds me of the old line:

> If we had some ham, we could have some ham and eggs, if we had some eggs.

If we are going to let this kind of compounded speculation stampede us into requiring quantitative aspartame labeling, where will we stop? This type of reasoning would as well justify us in requiring quantitative labeling of every possible ingredient because it might—you never can tell—produce a side effect in someone. I really do not think this approach serves the consumer well or reflects well upon our own deliberative abilities. It may be that FDA, after obtaining and reviewing the data it feels relevant, taking public comments, and weighing the matter under the laws as they exist, would require quantitative labeling of aspartame. Fine and good.

It may very well be that they may not require labeling of aspartame. If they do not, it will be for good and sufficient reasons. Thus far, they have not. But it is FDA that ought to be petitioned on issues like this, not Congress.

For these reasons I must oppose this amendment and ask my colleagues to oppose it as well.

Mr. HATCH. Mr. President, I reserve the remainder of my time.

Mr. MITCHELL. Mr. President, I rise today in opposition to Senator METZENBAUM's amendment to S. 484. That amendment would require quantitative labeling of aspartame, or NutraSweet, on soft drink containers.

I am not opposed to quantitative labeling in principle. But because this is an extremely complex and controversial issue, I believe it deserves a more complete hearing before the Senate Committee on Labor and Human Resources before it is brought before the full Senate for a vote. I am also concerned that this amendment may jeopardize the passage of the saccharin legislation which is supported by a majority of both Houses of Congress.

Serious questions about the safety of aspartame use remain unanswered. It is generally acknowledged that the FDA's initial testing of aspartame was inadequate; in 1980 an inhouse Scientific Board of Inquiry at the FDA issued a split decision on the question of aspartame approval.

The Centers for Disease Control [CDC] in Atlanta has been conducting a study of consumer complaints associated with the consumption of aspartame. The CDC concluded that the consumer complaints did not provide

enough cause for removing NutraSweet from the market, but they did suggest further studies. I support this recommendation.

There is evidence that the unlimited use of aspartame may be harmful to certain people under specific conditions. For that reason, I urge Senator HATCH to schedule additional hearings in the Senate Labor and Human Resources Committee on the issue of quantitative labeling of NutraSweet for soft drinks. I also encourage the FDA to continue to test this additive to determine whether individuals are likely to experience side effects from NutraSweet.

I look forward to the results of additional examination of this issue by the Congress, the FDA and the Centers for Disease Control.

● Mr. LEVIN. Mr. President, because there is an opportunity for the FDA to administratively require quantitative labeling of aspartame and this amendment will establish an important precedent without adequate purpose, I will vote against the Metzenbaum amendment.

The Food and Drug Administration is the better forum to first consider whether quantitative labeling is necessary after hearings and public comment. Furthermore, unless American consumers know what the "acceptable daily intake (ADI) of aspartame is, quantitative labeling is not widely useful.

While I am voting against the amendment proposed by Senator METZENBAUM for the above-mentioned reasons, I am open to considering some action similar to this in the future, particularly if the administrative process becomes bogged down or if such process shows that action such as this is needed.

Mr. METZENBAUM. Mr. President, how much time remains?

The PRESIDING OFFICER. Seventeen minutes, 20 seconds remain to the Senator from Ohio.

Mr. METZENBAUM. Mr. President, I ask for the yeas and nays.

The PRESIDING OFFICER. Is there a sufficient second? There is a sufficient second.

The yeas and nays were ordered.

Mr. METZENBAUM. The Senator from Ohio is not saying, "Do not use aspartame."

I am saying I do not know enough to make that kind of an assertion.

I do know enough to know that serious questions have been raised regarding this product.

Mr. President, I yield to the Senator from Louisiana.

Mr. LONG. Mr. President, I have not discussed this matter with the Senator previously, but I have received a letter recently from a person who is well known to me and whose word is impeccable, as far as I am concerned.

This person told me that she had been dieting and she had been using diet drinks with aspartame in it.

She said she found her memory was going. She seemed to be completely losing her memory. When she would meet people whom she knew intimately, she could not recall what their name was, or even who they were.

She could not recall a good bit of that which was going on about her to the extent that she was afraid she was losing her mind and was going to have to go to a mental institution. In due course, someone suggested that it might be this NutraSweet, so she stopped using it and her memory came back and her mind was restored.

Mr. President, that is a story I know to be completely true. This person enclosed some clippings from the New York Times which reported complaints from other people having similar types of experiences.

So, while I am sure that story might not be typical of the use of this product, it is a true story that I know about.

Mr. METZENBAUM. As a matter of fact, Mr. President, I would like to respond to the distinguished Senator from Louisiana that it is not atypical. As a matter of fact, we have received a number of letters from doctors reporting similar developments. We are aware that there are many other reports that have come into the Food and Drug Administration along the same line.

Nobody has conclusive evidence, but there is no question that there have been hundreds of instances of people who have suffered loss of memory, headaches, dizziness, and other neurological symptoms which they feel are related to aspartame. More studies are necessary. We hope to see that they get done.

But on this amendment, I am saying to the Senator openly that there are enough cases of this kind that it certainly seems to this Senator that we are not doing too much if we just say, "Tell the people at least how much is in the can."

Mr. LONG. Mr. President, if the Senator will yield further.

Mr. METZENBAUM. I certainly do yield.

Mr. LONG. The revelations about smoking and cancer came only after people had been smoking a long time. The Senator from Louisiana gained the impression that a young person starting smoking had no immediate indication of cancer connected with it. It was only when such a person had been smoking about 20 years that he began to come down with lung cancer, heart disease, and various other health problems resulting from smoking. No one can predict what this drug is going to do to people over a period of time.

There it is out on the market and people are consuming it by the tons. We know from reliable testimony of people who have used the product that there are many situations where people have had their health very adversely affected.

As the Senator indicates, only the good Lord knows what this thing is going to show over a period of time. It may well be that we may see many brain tumors and goodness knows what else associated with the product. I believe the Senator is only trying to say that at least we ought to have records to show what these people are consuming.

Mr. METZENBAUM. That is all. Put it on the can. There are a thousand-and-one other things on the can. We give them 18 months to modify the can. I cannot see any reason for opposition to this amendment. If I were coming in here and proposing that they not be permitted to use it, I could understand a battle on that. I am not saying that. I am just saying tell the people how much is in the can. What is so terrible about that and why so much lobbying is taking place against it is beyond my comprehension.

Mr. LONG. Mr. President, I appreciate the Senator's argument. The Senator has an amendment?

Mr. METZENBAUM. I do have an amendment.

Mr. LONG. I shall vote for the Senator's amendment. I think he is right.

Mr. METZENBAUM. Mr. President, I am very grateful to the Senator.

Mr. President, I say to the Senate that the FDA in 1981 placed a limitation of 20 milligrams of aspartame per kilogram of body weight. But the consumption was increasing so fast that the FDA put it up to 50 milligrams.

I do not know the right answer. I cannot give the answer to that. I know this: when they were originally talking about using aspartame, they were not talking about using it in soft drinks; they were talking about using it in other products, not liquid products of that kind. The amount they were talking about using was a small amount. It took many people by surprise when it was learned that they were going to use it in soft drinks and the consumption was significantly increased by including it in soft drinks.

There is no secret about the fact that many people who are on diets find that it is easier to drink a soft drink—it satisfies their appetite—rather than eat food. And they drink diet drinks. I cannot tell you how many, but I have been in the presence of people who, at one meal, have taken three or four cans of a soft drink, a diet drink, and what else they consume during the day, I do not know.

I say to my colleagues, Mr. President, we do not have anything to lose, the soft drink industry does not have anyting to lose. But there is a chance that there is very much to be gained if we adopt this amendment. I sincerely hope that we do so, but my guess is that the lobbyists have done their job and done it well.

Mr. NICKLES. Will the Senator yield for a couple of quick questions?

Mr. METZENBAUM. Absolutely.