WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
AT WASHINGTON UNIVERSITY MEDICAL CENTER

DEPARTMENT OF PSYCHIATRY

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Senator Howard M. Metzenbaum
United States Senate
140 Russell Senate Office Building
Washington, D.C. 20510

Dear Senator Metzenbaum:

I have been asked to update the Committee on my position regarding the several neurotoxicology issues that I and other neuroscientists presented before the Public Board of Inquiry (PBOI) on aspartame (Nutrasweet) in 1980. Three separate neurotoxicity issues were focused upon at the PBOI, one pertaining to the neurotoxic properties of aspartate (a major component of the Nutrasweet molecule), another to the neurotoxic properties of phenylalanine (the other major component of the Nutrasweet molecule) and the third to brain tumors. I will discuss the status of each issue as I see it today.

1. Aspartate neurotoxicity.

Aspartate (Asp) and the related compound, glutamate (Glu), are present in high concentration in the brain where they serve as excitatory neurotransmitters and participate in much of the information processing that occurs in the mammalian central nervous system. Paradoxically, these substances have striking neurotoxic potential--if allowed to have sustained contact with receptors on the exterior surface of the nerve cell, they literally excite the cell to death. The reason they do not manifest neurotoxic activity under ordinary circumstances is that they are synthesized and contained inside the nerve cells and are emitted outside only in tiny amounts for transmitter purposes; after transmitting a signal (exciting a neighbor cell), they are immediately (within milliseconds) taken back up into the cell.

Eighteen years ago, before the above information was known, my research group discovered that when Glu or Asp are administered orally to animals of various species including monkeys, they destroy nerve cells in certain parts of the brain. We found that Glu and Asp act in concert such that when ingested together they add to one anothers toxicity. Although we found animals at any age susceptible to Glu/Asp neurotoxicity, immature animals were much more sensitive than adults. Over the years neuroscientists have developed a much better understanding of this neurotoxic phenomenon. When Glu or Asp are ingested, they are absorbed into the blood very rapidly which causes blood

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levels of these amino acids to be transiently elevated. This, poses no hazard for most portions of the brain because Glu and Asp are prevented by blood brain-barriers from entering most regions of the brain. However, there are several small regions of brain that lack blood brain barriers, and blood-borne Glu and Asp freely penetrate these brain regions. This brings Glu and Asp in direct contact with receptors on the exterior surfaces of nerve cells and places such nerve cells in jeopardy of being excited to death. Nerve cells in immature brain are at greatest risk of being destroyed because important protective mechanisms are not yet functionally competent. In the neuroscience community today, this is commonly referred to as excitotoxic cell death and Glu and Asp are known as excitotoxins. The Glu and Asp contained in the brain are called endogenous excitotoxins and the Glu and Asp encountered in the environment are called exogenous excitotoxins.

The major source of human contact with exogenous excitotoxins is through the commercial food supply. Glu, in the form of its sodium salt, monosodium glutamate (MSG), is a very heavily used food additive. In 1969 when I first described the extreme sensitivity of the immature brain to the toxic effect of Glu, baby food manufacturers were adding very large amounts of Glu to baby foods. After I presented my research findings in testimony before the Senate Select Committee on Nutrition and Human Needs (1970), the Nixon white house worked out an agreement between FDA and the industries concerned whereby baby food manufacturers (who comprised a small fraction of the Glu market) would "voluntarily" quit adding Glu to baby foods. I applauded this part of the agreement but not the accompanying quid pro quo which was that FDA would continue to classify Glu as GRAS (generally regarded as safe) and would continue to allow other food manufacturers (comprising the bulk of the Glu market) to add unlimited amounts of Glu to "adult" foods destined to be ingested by consumers of all ages. Thus, Glu was taken out of baby foods but was not taken out of foods fed to babies. And, to this day, FDA still classifies Glu as GRAS, thereby conveying the dangerous message to parents that it is perfectly safe to feed Glu to babies.

Another major source of Glu and Asp in foods is hydrolysed vegetable protein (HVP). HVP is a mixture of Glu, Asp and other amino acids. It is because of its exceedingly high Glu concentration that HVP is used as a fond flavoring agent. After the baby food industry quit adding Glu to baby foods in 1970, they immediately began adding HVP in huge amounts in order to bring the Glu level (i.e., the flavor level) back to where it had been before. Throughout the 1970's I wrote letters, testified at hearings, etc. trying to get the baby food companies to quit adding HVP to baby foods and trying to get FDA to take a more responsible position. In the late 1970's, the baby food industry finally decided that their subterfuge was working more against them than for them so they opted for a clean image and quit adding excitotoxins to baby foods. No headway was made with FDA; the agency is still misleading and miseducating mothers into thinking that it is perfectly safe to feed Glu, HVP or any other excitotoxins to babies.

When Nutrasweet was first proposed as a sweetener, I was concerned because 50% of the Nutrasweet molecule is Asp and they were proposing to add it primarily to childrens foods and beverages (kool aid, coated breakfast cereal, etc.). In 1974, FDA approved Nutrasweet for such uses without even requiring the manufacturer to determine whether it has the kind of neurotoxicity that Asp was known to have. Therefore, I obtained some Nutrasweet in 1974, administered it orally to infant mice and demonstrated that it destroys nerve cells just like Glu and Asp do. I sent this evidence to FDA and filed a formal protest against their approval of the additive Because of information that was surfacing at that time implicating the manufacturer in apparent fraudulent practices, FDA stayed their approval of Nutrasweet and granted me the right to a hearing which was to take place after FDA completed their investigation of the manufacturer. The hearing finally took place in 1980 as a PBOI. In framing the issues for the PBOI, I insisted that the issue of Asp neurotoxicity not be considered in the narrow context of Asp alone but rather in the context of adding Asp to a food supply that already contains a similar excitotoxin (Glu) in amounts potentially dangerous for immature consumers.

In 1979 the Commissioner of FDA (Acting Commissioner, Sherwin Gardner) selected a 3 member panel of scientists to serve as judges for the PBOI. I strongly opposed the appointment of one of these judges on grounds of conflict of interest and lack of qualifications. The Commissioner arbitrarily overruled my objections allowing me no alternative but to participate in the PBOI under protest. As it turned out, the panel member whom I considered inappropriate was given a disproportionately large share of responsibility for deciding the Asp issue. The other 2 judges focused primarily on the brain tumor issue which they considered of overriding importance because it provided ample basis in itself for recommending disapproval of the additive. The result of this "division of labor" arrangement was that although all 3 judges signed the report, a single inappropriate judge decided that the Asp component of Nutrasweet did not pose any safety hazard. He based his decision on a consideration of Asp alone without regard to the real issue, i.e., is it safe to add Asp to the large amounts of Glu that are already adulterating the food supply?

My opinion regarding the status of the Asp neurotoxicity issue is that it was handled in an inappropriate manner by the PBOI panel; the real safety issue still remains unresolved and human young are being exposed to potentially dangerous and ever increasing amounts of Glu and Asp, both of which are exogenous excitotoxins that can rapidly destroy nerve cells in the developing brain. The amount of Glu being added to foods today is dangerous in itself; adding a second excitotoxin (Asp) to the same food supply increases the danger.

To put the issue in proper perspective, let me bring you up to date on other developments in the field of excitotoxicology. It is now becoming abundantly clear that endogenous excitotoxins (i.e., the Glu and Asp naturally present in the brain) are responsible for several very common types of brain damage that

afflict humans--for example, the brain damage that is associated with stroke, cardiac arrest and perinatal asphyxia (cerebral palsy). In these conditions there is a sudden release of Glu and Asp from cells in the brain coupled with paralysis of the mechanism for taking them back into the cell. If Glu and Asp are released from cells and not rapidly taken back up, they flood the excitatory receptors on the external surface of nerve cells and excite nerve cells to death. It has recently been shown that certain drugs which block the action of Glu and Asp at these excitatory receptors can protect the animal brain against damage associated with stroke, cardiac arrest or perinatal asphyxia. Thus, it is an ironic fact that today knowledgeable neuroscientists in many parts of the world are working fervently to develop methods for preventing endogenous excitotoxins from damaging the human brain, while other elements of society, including the FDA, are promoting and sanctioning the adulteration of foods with unlimited amounts of exogenous excitotoxins which are known to destroy nerve cells in the mammalian brain following oral intake.

2. Phenylalanine Neurotoxicity

I understand that the phenylalanine neurotoxicity issue is the major focus of the present hearings and that it is being addressed by other scientists. Therefore, I will just state my position without much explanatory background.

At the PBOI I argued that Nutrasweet would unnecessarily complicate and undermine the therapy of children who are homozygous for PKU and who must adhere to a low phenylalanine diet; for the parents of these children and their doctors, Nutrasweet is, at best, an enormous nuisance. I also pointed out that the screening programs which attempt to detect homozygous PKU victims at birth are not overly effective, there being approximately 30 % of such victims who escape detection. My opponents acknowledged this but argued that Nutrasweet would not contribute to the mental maldevelopment of these children because this maldevelopment already has irreversibly occurred before the child would be old enough to come in contact with Nutrasweet. I countered with the observation that babies can be seen all over the United States, even in pediatric hospital wards, sucking on baby bottles containing Kool Aid. This point was ignored, as were other relevant points I presented on the phenylalanine neurotoxicity issue.

I raised a very important issue concerning a small but not insignificant population of individuals (several thousand) who are called PKU variants. These people are found at birth to have a PKU-like defect but it is not severe enough to warrant the diagnosis of PKU, so the child is not stigmatized with the PKU diagnosis and is not placed on a low phenylalanine diet. When female PKU variants reach child bearing age, and become pregnant, they will not take special precautions to avoid Nutrasweet because they do not know they have a PKU-like illness. If such a person follows a normal diet during pregnancy, her blood phenylalanine levels will be high because of the partial PKU-like defect and her fetus will be exposed to even higher phenylalanine levels because phenylalanine blood levels are increased (approximately doubled) when phenylalanine is transfered across the placenta from the maternal to the fetal

circulation. Thus, even on a normal diet this mother will be exposing her fetus to amounts of phenylalanine that are approaching the toxic threshold, i.e., the threshold for causing mental retardation. All it would take to exceed the toxic threshold and assure that the fetus will be born severely retarded is for the mother to use Nutrasweet during pregnancy (hoping to avoid excessive weight gain). This is a clear cut example of mental retardation that could be anticipated and prevented by an enlightened regulatory establishment. Thus far, FDA has dealt with this problem by simply ignoring it.

It is also an exceedingly important question, but one that is more difficult to assess, whether Nutrasweet use during pregnancy by a person who is heterozygous for PKU might cause her fetus to be born less intelligent than otherwise might have been the case. This is an important issue because there are many PKU heterozygotes in the world who are unaware that they have the PKU trait. I trust others who are testifying at your hearings will address this issue.

Finally, there is another important point that was raised at the PBOI which may be relevant to the types of Nutrasweet-related consumer complaints that have been heard subsequently. Contrary to the claims of Nutrasweet proponents, ingesting phenylalanine as part of the Nutrasweet molecule is not the same as ingesting phenylalnine as part of a food protein molecule. There are several complex mechanisms that cause more phenylalanine to end up in the brain after Nutrasweet ingestion than would occur from ingesting the same amount of phenylalanine contained in food protein. Thus, humans who ingest large amounts of Nutrasweet are likely to have significant increases in brain concentrations of phenylalanine. Since phenylalanine feeds into important metabolic pathways which regulate the levels of several neurotransmitters in the brain, it is reasonable to expect that ingesting large amounts of Nutrasweet might have effects on the central nervous system. Incidentally, the vast majority of Nutrasweet consumer complaints that have come to my attention do pertain to the central nervous system. I doubt whether the thousands of lay citizens who have generated these complaints have thought it out ahead of time and conspired to make all of their complaints sound like their central nervous system is being affected. It should also be mentioned that effects such as menstrual difficulties are correctly interpreted as disturbances of the central nervous system since various Asp or phenylalanine-related neurotransmitters in the brain regulate the amount of pituitary hormones that circulate in the blood and control menstrual functions.

The fact that consumers have frequently complained of seizures in association with Nutrasweet ingestion warrants special attention. This was not a type of side effect that was anticipated or discussed at the PBOI. However, in retrospect it should have been. It is known from the PKU literature that, in addition to mental retardation, nearly 80% of untreated PKU patients have electroencephalographic evidence suggestive of epilepsy and over 30% have frank epilepsy. Placing such individuals on a low phenylalanine diet does not

reverse the mental retardation but it does ameliorate the manifestations of epilepsy. This suggests that influx of excess phenylalanine into the brain can make a person seizure-prone for as long as the influx continues. Thus, there is medical precedent for expecting that consumers might experience seizures in association with Nutrasweet ingestion.

3. Brain Tumors

This is an exceedingly complex topic which, unfortunately, has a history riddled with appearances of fraudulant practices by the manufacturer of Nutrasweet and ineptitude and/or malfeasance on the part of FDA officials. In the mid 1970's, when I reviewed the Nutrasweet record in preparation for the hearing I had been promised, I came upon a peculiar study which the manufacturer had submitted to FDA and which FDA had unquestioningly accepted as evidence for the safety of Nutrasweet. The study showed that in 320 Nutrasweet-fed rats there were 12 brain tumors whereas in a group of concurrent control rats which were not exposed to Nutrasweet, there were no brain tumors. Being a neuropathologist, I know that spontaneous brain tumors in laboratory rats are extremely rare. The archival literature documents an incidence not exceeding 0.6%. Since the above incidence in Nutrasweet-fed rats is 3.75%, this suggests that Nutrasweet may cause brain tumors and certainly suggests the need for additional in depth research to rule out that possibility.

The manufacturer had done an additional study and submitted it to FDA at the same time as the former study was submitted. The second study also showed a very high incidence of brain tumors in Nutrasweet-fed rats but in this study the control rats also had a similarly high incidence. This did not make any sense, unless both the control and experimental rats were exposed to a tumor promoting agent. A subsequent FDA investigation of the laboratories where these studies were conducted revealed appearances that the control and experimental animals may very well have been fed one another's chow in a sloppily randomized manner so that, in essence, all animals on the study may have been fed Nutrasweet during portions of the study. The judges at the PBOI agreed with me that the exceedingly high incidence of brain tumors in the Nutrasweet-fed rats of the first study and a similarly high incidence in all rats of the second study was a "bizarre" collection of data that could not be considered evidence for the safety of Nutrasweet.

There were other problematic aspects of the brain tumor data. In the pre-1975 records that I reviewed, it was clear that several competent pathologists had carefully examined the original microscopic slides from the first study and agreed that there were 12 brain tumors in the Nutrasweet-fed rats and zero brain tumors in the controls. When the FDA conducted a task force investigation of these laboratories in 1975, they singled out these studies for further investigation and ordered that all laboratory records, including microscopic slides etc. be impounded under FDA seal. Several years later when a group of pathologists (EUREP) was sent to authenticate these studies, they could not find the microscopic slides. The EUREP pathologists were finally

taken to a laboratory where the slides were not supposed to be and there they found some but not all of the original slides. Clearly they had not been kept under FDA seal and by mysterious coincidence the slides that were finally presented to the EUREP pathologists contained evidence for 11 brain tumors in Nutrasweet-fed rats and 1 tumor in controls. It is important to recognize that if there are zero tumors in the controls, it is very difficult to argue that the tumor incidence in the control and Nutrasweet-fed rats is the same. But if there is 1 tumor in the control group, it is possible with statistical acrobatics to reach the conclusion that the incidence is the same. And, indeed, this is exactly the argument that the manufacturer and FDA Bureau of Foods pressed at the PBOI. They accepted the finding of 1 brain tumor among the controls even though the authentic record showed zero brain tumors in controls, then they proceeded to break down the animals into smaller and smaller sub groups according to sex, dose level etc and finally the 1 brain tumor in one sub group of control animals appeared to be not significantly different from 2 or 3 tumors in each of the experimental sub groups. I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ. of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the Nutrasweet-fed rats. This reinforced his impression that they had been caused by some tumorigenic agent since spontaneous brain tumors are not only rare in laboratory rats but when they do occur they are usually not so large. Dr. Lampert is now deceased; he died in 1986 of cancer. At the time he participated in the PBOI, he was the President of the American Association of Neuropathologists. I had nominated him to serve on the PBOI panel.

If Nutrasweet is a tumorigenic agent, one possible mechanism would be that its breakdown product (DKP) might be responsible. Therefore it is very important that the DKP breakdown product be studied separately to rule out any tumorigenic potential. This is particularly important if Nutrasweet is to be used in beverages since it breaks down much more readily in beverages. The manufacturer did conduct one study purporting to show that DKP has no tumorigenic potential but this was also a study riddled with appearances of fraud and/or incredibly sloppy and unreliable laboratory practices. In 1977, FDA sent a field team to investigate the manufacturer's laboratory where this study was conducted and they found evidence suggesting that the rats in the DKP study may not have actually been fed much if any DKP. The records suggested that the feed had been offered to the rats in powered form with the DKP added in large chunks. Rats are smart enough to push aside the chunks of DKP and eat the powered chow. Remarkably, one of the research technicians who worked on

that study photographed a sample of the feed to show how large the DKP chunks were and she left the photograph in her record book. Another person employed in the laboratory at the time was known to have been concerned that the feed was not being properly mixed. That person had moved to a new job with another manufacturing firm. The FDA inspectors called him at the new site and he volunteered information by phone that he did remember the DKP study and did believe the DKP chunks were large enough that the rats could select the chow and avoid the DKP. Then the inspectors went to the new job site to formally interview him and they noticed that someone from G.D. Searle had signed in immediately before them. When they reached the interviewee, he was unwilling to talk to them. When they tried to interview an individual who had been director of the laboratory in which that study was performed, he declined to talk to them on advice from his lawyer. When they interviewed the individual who mixed the feed for the DKP study over a two year period of time, he could not remember anything about the study. This information was sent as a field inspection report to the FDA Bureau of Foods where it was buried. The inspection team had not proven that the feed sample in the photograph was definitely the feed fed to the animals so Bureau of Foods concluded that there was no evidence of wrong doing. Also they concluded that this DKP study adequately proved that DKP has no tumorigenic effects.

I am intimately familiar with the details of the above circus performance because, although the FDA field inspection had been done secretly and FDA intended for the field inspection report to remain secret, I was informed by a prior FDA official that the inspection had taken place and was advised to seek the report through freedom of information channels. It was difficult to obtain, and at one point they flatly refused to supply me with a copy of the photograph of chunky feed claiming that it was property of the manufacturer. However, finally I did get the full report and a copy of the photograph. At the PBOI neither G.D. Searle nor FDA Bureau of Foods volunteered any information about the field inspection although both of them, as participants in the PBOI, were bound by FDA rules to provide the PBOI record with all information relevant to the safety of Nutrasweet. Since they were not forthcoming with this information, I asked for permission to introduce it at the time of the PBOI. The PBOI judges listened to a brief preliminary presentation then interrupted me saying that they needed to have an intermission. They returned from the intermission and said that they would not attempt to evaluate this information but suggested that I might want to air it before some other type of tribunal.

As you know, the PBOI judges unanimously recommended that Nutrasweet <u>not</u> be approved. However, the Commissioner of FDA arbitrarily swept aside the PBOI recommendations and summarily approved Nutrasweet for various foods, then a year or so later for the beverage industry and now I understand the agency intends to approve it for baked goods (it also breaks down rapidly when heated). In his written decision approving Nutrasweet, the Commissioner of FDA argued quite incorrectly that the spontaneous incidence of brain tumors in Sprague Dawley rats is much higher than 0.6%. In spurious support of this

conclusion he cited several irrelevant and/or unreliable studies which he considered more compelling than the appropriate scientific evidence cited by the PBOI judges. Also, he biased his analysis of the brain tumor data by assuming the presence of a primary brain tumor in the control rats even though the authentic record showed no such tumor.

Although there is one study that has been reported since the PBOI which claims to have demonstrated that neither Nutrasweet nor DKP has tumorigenic activity, I am not very impressed with this study. It was conducted by the Ajinomoto Co. of Japan which is one of the world's largest manufacturers of Monosodium glutamate and hydrolyzed vegetable protein and a company which I believe has had a contractual relationship with GD Searle to manufacture Nutrasweet. This study, which was reported sketchily in a journal of poor quality, pertains to a different strain of rat than was used in the GD Searle studies (Wistar instead of Sprague Dawley) and therefore has not adequately addressed the questions raised by the GD Searle studies. The only way to address those questions is to conduct studies that use the same strain of rat and carefully control all experimental variables which were not carefully controlled in the GD Searle studies. One wants to know why Sprague Dawley rats exposed to Nutrasweet had a 3.75% incidence of brain tumors in the GD Searle study. Would another study of Sprague Dawley rats, if properly conducted, show the same thing or would it cleanse the record and show that there is a very low incidence of brain tumors in both the Nutrasweet-fed and control rats? The record has not been set straight by the Ajinomoto study on Wistar rats briefly reported in a journal which is not rigorously refereed (and whose editor is financially dependent on the food industry). The FDA Commissioner's office stated at the time he approved Nutrasweet that he was not relying on the newly reported Ajinomoto study but rather was satisfied with the original GD Searle data on Nutrasweet and did not believe any further studies are necessary. I am not satisfied with the original GD Searle studies. The record shows them to be of exceedingly poor quality and the only way to overcome such a record is to have the key studies repeated, preferably by an independent laboratory of the highest possibly integrity.

Sincerely,

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Professor of Psychiatry and Neuropathology

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