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COMMITTEE OF LABOR AND HUMAN RESOURCES

"NUTRASWEET: HEALTH AND SAFETY CONCERNS"

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Statement for the Labor and Human Resources Committee, U.S. Senate

I have considerable concern for the increased dissemination and consumption of the sweetener, aspartame (1-methyl N-L-a-aspartyl-L-phenylalanine) in our world food supply. This artificial dipeptide is hydrolyzed by the intestinal tract to produce L-phenylalanine which in excess is a known neurotoxin. Normal humans do not metabolize phenylalanine as efficiently as do lower species such as rodents and thus most of the previous studies in Aspartame effects on rats are irrelevant to the question, "does phenylalanine excess occur with Aspartame ingestion?" and if so "will it adversely affect human brain function?"

Preliminary studies in my laboratory provide tentative positive answers to both questions. Many studies of both acute and chronic ingestion of 34 mg Aspartame/kg/day have demonstrated a two to five fold increase in semi-fasting blood phenylalanine concentrations (from approximately 50 to 250 μM) without concomitant increases in tyrosine or other aminoacids. The degree of increase by normal humans depends on several variables including the efficiency of gut transport, liver utilization, and growth rates. It was thought by many scientists and clinicians that this degree of blood phenylalanine increase would not affect brain function. However, currently available information indicates that this is not true.

1) In the developing fetus such a rise in maternal blood phenylalanine could be magnified four to six fold by the concentrative efforts of the placenta and fetal blood brain barrier. Thus a maternal phenylalanine of 150 μM could reach 900 μM in the developing fetal brain cell and this concentration kills such cells in tissue culture. The effect of such an increased fetal brain concentrations in vivo would probably be much more subtle and expressed as mental retardation, microcephaly, or potential certain birth defects.

2) In the rapidly growing post-natal brain (children of 0-12 months) irreversible brain damage could occur by the same mechanism.

3) In the adult we have found that changes in blood phenylalanine in these concentration ranges are associated with slowing of the electroencephalogram, and prolongation of cognitive function tests. Fortunately, these effects on the mature brain are reversible but provide clear evidence for a negative effect on sensitive parameters of brain function.

In view of these new (and confirmation of old) research findings I suggest the following:

1) Immediate quantitative labeling of all aspartame-containing foods, so the consumer will know how much phenylalanine he/she is ingesting.

2) Declare an immediate moratorium on addition of aspartame to more foods and remove it from all low-protein beverages, foods, and children's medications.

3) Provide funds not controlled by industry to:

   a) Allow active surveillance for potential side-effects of aspartame on newborns whose mothers dieted with Nutrasweet® (Aspartame)-containing foods.

   b) Allow active evaluation of other users whose complaints cannot be adequately studied at present.

   c) Clarify the dose relationship and mechanisms by which L-phenylalanine affects human brain function.

Respectfully submitted

Louis J. Elsas II M.D.

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Director, Division of Medical Genetics
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Senator METZENBAUM. Dr. Elsas, since Senator Hatch saw fit to go into the funding question, I will ask you, are your studies funded by industry?

Dr. ELSAS. No, sir. I had a research grant three years ago, for three years, from the March of Dimes, to study the effects of phenylalanine on human brain function. When the political issue got to aspartame, the society decided not to refund that. So all of the funding that is going on now—and the reason it is so slow has been through my own division's efforts, personal funds, and university-based funds.

Senator METZENBAUM. What do you think of our present system for funding scientific research?

Dr. ELSAS. I think the NIH is superb. I think there is a lot of concern about how industry and the FDA interact, where industry is made responsible for developing the data to support its own contentions. There is not a broad enough scientific base, such as an RFA, as we call it at NIH—research funds available—requesting input from the whole scientific community, stating that funds are available to investigate a certain area. In that way, you would get in an unbiased approach—what the questions are which we need to ask? That is the problem here today. The questions about phenylalamine effects on human brain function have not been asked. So we have spent millions of dollars through our current system on mostly irrevelant experiments without approaching those particular questions.

Senator METZENBAUM. What about the advertising campaign that NutraSweet puts on, and are you concerned about that?

Dr. ELSAS. Yes, sir.

Senator METZENBAUM. In what way?

Dr. ELSAS. I am mostly concerned that it gives the false impression that NutraSweet is good for you, that it is nature's best, and that it might even be good for children to take. A lot of the ads recently have shown children with the little ying and yang NutraSweet thing on it, making it sound like you should go with your mommy to the grocery store and look for that, and be sure that you buy that because it is real sweet and good.

Senator METZENBAUM. Can you tell the Committee about your own experiences with the International Life Sciences Institute?

Dr. ELSAS. Yes, sir. It was not good.

Senator METZENBAUM. Who is that group, can you tell us?

Dr. ELSAS. Well, Dr. Dews is right here; he can probably give you more personal information about it, because I have never gotten any feedback from them. But I was asked after issuing concerns both privately and then publicly on "Nightline" to give them a specific protocol for how I would approach these concerns. I did this. I wrote it up completely in a research grant format; submitted it through ILSI for their review, and basically, got a few phone calls from Dr. Dews over a prolonged period of time, stating that they had problems, but without ever a written peer review of criticism.

So I basically never got funded; that is the bottom line. And the ideas are now reappearing three years later in other places funded by industry.

Senator METZENBAUM. ILSI is pretty much the coordinating group for funding in the food and beverage industry, including pops, carbonated drinks, NutraSweet itself; is that correct?

Dr. ELSAS. As far as I know, that is correct, sir. I am not an expert on ILSI; I have repressed that experience.

Senator METZENBAUM. It is my understanding that Dr. Pardridge has to catch a plane, so I am going to pass on to him. But I appreciate your testimony, Dr. Elsas, and I am only sorry Senator Hatch was not here to hear you comment on the fact that—at least, the inference; it is not a fact—that if the information or the research is not going to be supportive of their position, that sometimes one does not get supported by organizations such as ILSI, NutraSweet and others.

Do you think that general conclusion of mine might be inappropriate, or appropriate?

Dr. ELSAS. Sir, I think that is very cogent and appropriate.

Senator METZENBAUM. Thank you very much.

Would you agree with that, Dr. Wurtman?

Dr. WURTMAN. Yes, sir.

Senator METZENBAUM. Thank you.

Dr. Pardridge, we are happy to hear from you, sir.

Dr. PARDRIDGE. Thank you, Senator, and thank you for having me.

I am a Professor of Medicine at the University of California, a practicing endocrinologist, and I have been doing neuroscience research on the blood-brain barrier transport of phenylalanine and other substances since 1970.

I believe in the discussion this morning, there are three key scientific food policy questions that have really not been properly illuminated.

The first question is the dosage problem. We are led to believe by the FDA this morning that the typical consumer will have 2 to 4 milligrams per kilogram of aspartame per day; that the 99th percentile intake is 34 milligrams per kilograms per day; and that the advisable daily intake or ADI is 50 milligrams per kilogram per day.

Now, the layperson sitting in the audience is really is in no position to analyze these esoteric numbers. But if we put it in a different context and recognize that 50 milligrams per kilogram per day is equal to 5 servings of NutraSweet per 50-pound body weight, we can see that children, owing to their reduced body weight, are at great risk for overconsumption of NutraSweet.

All one has to do in this room is look up at that chart and ask yourself if a 50-pound or 60-pound 7 year-old is going to consume 5 or 6 servings of that per day. If they are, then they have consumed 50 milligrams per kilogram per day, or the advisable daily intake.

Now, an 11-year study in the literature has already shown this, that the average 7-to-12-year-old, when made freely available to products like that, consumes 5 servings per 50-pound body weight per day, and up to 77 milligrams per kilogram per day.

Senator METZENBAUM. That is the average?

Dr. PARDRIDGE. The average in children is the ADI—5 servings per 50-pound body weight. Ask yourself: Would an average child have 5 servings? I think the answer is yes.

Another study by Porikos in obese subjects showed that the average intake was 20 milligrams per kilogram per day, or 2 servings per 50-pound body weight, and that obese adults consume up to 36 milligrams per kilogram per day, even in the face of that high body weight.

Now, if you accept the premise of the first question, that some individuals and in fact many children consume near the advisable daily intake of 50 milligrams per kilogram per day, then you must ask yourself what level of increase in blood phenylalanine will be concomitant with that ingestion of NutraSweet. And the answer is that your blood phenylalanine will rise three- to four-fold. That is not 10 percent or 20 percent. That is 300 to 400 percent. And this study has been done by Drs. Stegink and Filer, which was funded by the industry.

If you now accept that many individuals, particularly children, consume 50 milligrams per kilogram per day, or 5 servings per 50-pound body weight per day, and that they enjoy a four-fold increase in their blood phenylalanine, the third question that must now be addressed is, are there any untoward effects on the human brain that are associated with a four-fold increase in phenylalanine, bearing in mind that this molecule is a known neurotoxin?

And three studies come to mind. One study shows that when blood phenylalanine in pregnant mothers is increased five-fold, there is a 10-point drop in the I.Q. of the baby born of that mother.

Senator METZENBAUM. A 10-point drop in what?

Dr. PARDRIDGE. In the baby born of that mother; a 10-point drop in I.Q. of the baby born of that mother.

Senator METZENBAUM. Of I.Q. All right.

Dr. PARDRIDGE. A second study shows that if you measure choice reaction time, a test of higher cognitive function in humans, that when their blood phenylalanine is increased six-fold, there is a 10 percent shift in your ability to make a key decision before a video screen.

And a more recent study by Dr. Elsas has shown that there are quantitative changes in the human electroencephalogram when the blood phenylalanine is raised three-fold—something that clearly will happen in children who consume near 5 servings per 50-pound body weight.

So if I may summarize, phenylalanine is a known neurotoxin, and the food industry added nearly 8,000 tons of aspartame to the food supply in 1986, which amounts to approximately 8 million pounds of phenylalanine added to our food supply in a single year.

The consumption of aspartame has increased exponentially since its introduction in 1981. The 1986 consumption of aspartame in the United States was equal to nearly 22 percent of the 1986 consumption of refined sugar when one allows for a 200-fold increase in sweetener potency of aspartame relative to sugar.

With the enormous selective infusion of phenylalanine into the food supply, the key questions before the United States Congress and other scientific and medical organizations are whether selective increases in the blood phenylalanine level on the order of 200 micromolar or four-fold above normal, are to be expected with liberal intake of aspartame, and whether blood phenylalanine in-

creases of this magnitude have untoward effects on the human brain.

Thank you.

[The prepared statement of Dr. Pardridge follows:]

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Statement of William M. Pardridge, M.D. Before
the United States Senate Committee
on Labor and Human Resources:

I have concerns regarding the widespread utilization of aspartame as a common nonnutritive sweetener (1, 2). Aspartame is a protein-like substance that is composed of two amino acids (aspartic acid and phenylalanine) and methanol. I believe the aspartic acid and methanol portions of aspartame are harmless. However, aspartame usage in high doses can lead to significant increases in blood phenylalanine. It is this increase in blood phenylalanine following aspartame consumption that is of concern to me. The basis for my concerns are three-fold.

1. Although industry estimates of individual aspartame intake are approximately 10 mg/kg per day, and the FDAs advisable daily intake (ADI) is 50 mg/kg per day, I believe that a significant portion of the population, particularly children, will consume upwards of 50 mg/kg per day, or approximately the ADI. In layman's terms, a dose of 50 mg/kg per day is approximately 5 servings per 50 lb body weight per day. While it is true that most 150 lb adults will not come close to consuming 15 servings per day, I believe that children, owing to their reduced body weight, will consume up to five servings per 50 lb body weight per day and approximate, or exceed, the ADI. Indeed 11 year-old studies have shown that when 7-12 year-old children have free access to a liberal supply of aspartame-sweetened products in their diet, their average consumption is 50 mg/kg per day and ranges up to 77 mg/kg per day (3). Since aspartame can be found in soft drinks, fruit juices, breakfast cereals, gelatin, puddings, milk shakes, and a whole host of other products, it is not surprising that a typical 7-12 year-old child may consume up to five servings per 50 lb body weight per day. The industry notion that children consume much less than 10 mg/kg per day must be categorically rejected, when it is recognized that the consumption of a single 12-oz can of cola by a 50 lb 7-year-old is already a dosage of 10 mg/kg per day.

2. If it is granted that many children and some adults will consume up to 50 mg/kg per day of aspartame (i.e., about five servings per 50 lb body weight per day) then it should also be recognized that data in the medical literature indicate that this dosage of aspartame will result in a doubling of blood phenylalanine in normal individuals and at least a tripling of blood phenylalanine in subjects who are heterozygous for the phenylketonuric (PKU) trait (4). The estimate of individuals with PKU heterozygocity (i.e., the condition associated with slow metabolism of dietary phenyalalanine) is believed to range anywhere from 4-20 million individuals in the United States (5). Since the normal blood phenylalanine concentration is approximately 50 µM, the blood phenylalanine level will rise to 100-150 µM in individuals who consume approximately 50 mg/kg per day of aspartame (4).

3. My third concern is that there are data in the medical literature which indicate that a tripling of blood phenylalanine to the level of approximately 150-200 µM concentrations may have untoward effects on the human brain. One study suggests that mothers who have a blood phenylalanine concentration of 250 µM bear offspring with a 10 point drop in IQ (5). Another study indicates that when blood phenylalanine is increased to the 250 µM concentration, there is a 10% change in choice reaction time, a test of higher cognitive function in humans (6). More recently, another study has shown that when blood phenylalanine is increased into the range of approximately 150-200 µM, there are quantitative changes in the electroencephalogram in humans (7).

Phenylalanine is a known neurotoxin, and the food industry added nearly 8,000 tons of aspartame to the food supply in 1986, which amounts to approximately 8 million lb of phenylalanine. The consumption of aspartame has increased exponentially since its introduction in 1981. The 1986 consumption of aspartame in the United States was equal to nearly 22% of the 1986 consumption of refined sugar (allowing for a 200-fold increase in sweetener potency of aspartame relative to sugar). With this enormous selective infusion of phenylalanine into the food supply, the key questions before the United States Congress and other scientific and medical organizations are whether <u>selective</u> increases in the blood phenylalanine level on the order of 200 µM are to be expected with liberal intake of aspartame, and whether blood phenylalanine increases of this magnitude have untoward effects on the human brain.

Yours very truly,

William M. Pardridge, M.D.
Professor of Medicine

References

1. Pardridge, W.M. Potential effects of the dipeptide sweetener aspartame on the brain, in Wurtman R.J., Wurtman J.J. (eds.): Nutrition and the Brain, New York, Raven Press, 1986, vol 7, pp 199-241.
2. Pardridge, W.M. The safety of aspartame. JAMA 1986; 256:2678.
3. Frey, G.H. Use of aspartame by apparently healthy children and adolescents. J. Toxicol. Environ. Health 1976; 2:401-415.
4. Filer, L.J. Jr., Stegink, L.D. Effect of aspartame on plasma phenylalanine concentration in humans, in Wurtman R.J., Ritter-Walker E. (eds.): Dietary Phenylalanine and Brain Function, Cambridge, Mass., Center for Brain Sciences and Metabolism Charitable Trust, 1987, pp 25-56.
5. Levy, H.L., Waisbren, S.E. Effects of untreated maternal phenylketonuria and hyperphenylalaninemia on the fetus. N. Engl. J. Med. 1983;309:1269-1274.
6. Krause, W., Halminski, M., McDonald, L., et al. Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria: A model for the study of phenylalanine and brain function in man. J. Clin. Invest. 1985;75:40-48.
7. Elsas, L.J., Trotter, J.F. Changes in physiological concentrations of blood phenylalanine produce changes in sensitive parameters of human brain function, in Wurtman R.J., Ritter-Walker E. (eds.): Dietary Phenylalanine and Brain Function, Cambrideg, Mass., Center for Brain Sciences and Metabolism Charitable Trust. 1987, pp 263-273.

Senator METZENBAUM. Dr. Pardridge, let me just learn a little bit about yourself. You are a Professor of Medicine at the University of California?

Dr. PARDRIDGE. Yes, sir.

Senator METZENBAUM. Can you tell us some more about yourself? You are in the Division of Endocrinology and Brain Research Institute.

Dr. PARDRIDGE. I am a member of the Brain Research Institute. I am the director of the Blood-Brain Barrier Laboratory. The blood-brain barrier is more or less the gatekeeper of the brain, that allows phenylalanine and other amino acids into the brain. I am a practicing internist and endocrinologist. I perform clinical rounds in the UCLA Medical Center. And I run a very active laboratory that consists of 15 individuals, all working on various aspects of blood-brain barrier.

Senator METZENBAUM. And did ILSI once fund a study for you?

Dr. PARDRIDGE ILSI in 1985 funded a study which showed that the human blood-brain barrier is nearly identical to the rat blood-brain barrier in terms of sensitivity to amino acid blockade by increased blood phenylalanine. That allowed extrapolation of Dr. Wurtman's studies in rats to the human condition.

Senator METZENBAUM. And have you had any other private funding?

Dr. PARDRIDGE. From ILSI?

Senator METZENBAUM. ILSI or any other group.

Dr. PARDRIDGE. No. I submitted two other grants to ILSI, but they were turned down. But I do not see how these funding issues are the important questions. The important questions are the dosage problem that I have raised. We have to get away from this 2 to 4 milligrams per kilogram idea that the FDA has been foisting on people and recognize that children will have about 5 or 6 servings of that stuff per day, and that they are going to get up into the ADI, and that the blood level of phenylalanine is going to rise, and that is going to have untoward effects on the human brain.

Senator METZENBAUM. Your point is that accepting the FDA's own figures as to where it is dangerous, that that is a reality of life today for the average consumer of aspartame, and that therefore there is an at-risk problem; am I understanding you correctly?

Dr. PARDRIDGE. Not only the consumer, but medical organizations. The American Diabetes Association is led to believe that a typical 7 year-old diabetic child on insulin, avoiding sugar, will consume considerably less—10-fold less—than the advisable daily intake. I ask if that 7 year-old diabetic child, who weighs 50 to 60 pounds, is he going to have 5 or 6 of those products, one each of those products. If he is, then the ADA and the FDA are wrong. The consumption of this substance can be considerably high, particularly in children.

Senator METZENBAUM. What do you think we ought to do?

Dr. PARDRIDGE. I think there should be quantitative labelling of all products immediately, so that physicians when confronted with a possible aspartame-related problem, can compute through a careful nutritional history the amount of milligrams per kilogram per day ingested. If it is 5 to 10 milligrams per kilogram, then I would not attribute that symptom complex to aspartame ingestion. If it is

40, 50, 60 milligrams per day or above, then I would seriously investigate the role of aspartame in their clinical problem.

Senator METZENBAUM. Dr. Elsas, I gather you would agree also that labelling would be a major asset in coping with this problem while clinical research is provided for?

Dr. ELSAS. Yes, sir, I do.

Senator METZENBAUM. And Dr. Wurtman?

Dr. WURTMAN. Yes, sir, I do.

Senator METZENBAUM. Thank you very much.