STATEMENT OF DR. JACQUELINE VERRETT, FORMER TOXICOLOGIST, U.S. FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. VERRETT. Thank you very much, Senator Metzenbaum.

I appreciate the opportunity of coming before you today, and perhaps I can straighten out what I think are some of the basic problems in this whole controversy, going back to the initial data that were received at Food and Drug.

Do we have time for me to read my whole statement?

Senator METZENBAUM. How much time will that take?

Dr. VERRETT. I have not timed it, but probably seven minutes.

Senator METZENBAUM. That will be all right.

Dr. VERRETT. From 1957 through 1977, I was employed as a biochemist/toxicologist in what is now designated as the Center for Food Safety and Applied Nutrition at FDA.

During this time, my duties were twofold—first, an evaluation of experimental data submitted to FDA in support of the safety of a wide variety of chemicals and processes such as irradiation that were intended for food additive use both directly and indirectly, as well as data pertaining to various contaminants in the food supply, such as mycotoxins and pesticides, and also of some drugs.

The second aspect of the work was a variety of research pertinent to FDA's mission and for the most part, devoted to the overall toxicity and more specifically to teratogenic—that is, birth-deforming—capabilities of several hundred substances that may be broadly classified as food additives or as food contaminants.

In the early 1970s, I examined the animal studies submitted by G.D. Searle on aspartame prior to the initial approval by FDA in 1974. While I cannot recall any specific examples, it was my overall impression that these studies raised numerous questions in a number of areas that needed to be resolved before approval of aspartame for any food additive use.

And this is not in my statement as written, but I would like to add here to make things clear, the fact that the initial submission to which I am referring as were most petitions submitted to Food and Drug, was in a summary form. We did not see individual records and so forth, and it already had conclusions drawn.

In 1977—and this is after the investigation of Searle—I served as a member of an FDA team from the Bureau of Foods which was charged with examining three studies—specifically, the rat long-term study of the DKP, diketoperpazine, which is a breakdown product of aspartame—and two aspartame teratology studies in mice and rats. We were doing this to determine if they were authentic.

We were instructed to incorporate the findings of the FDA task force investigation—which I will refer to now as the Bressler Report—and to determine whether alterations and adjustments to the data engendered by the inclusion and consideration of all of these discrepancies resulted in any significantly different results from those originally presented in the original Searle submission.

This authentication was hence intended to verify that the submitted data had not been altered; that it reflected the actual outcome of the study, and that it did not change substantially, particularly in a statistical sense, the various parameters from which the conclusion of safety had been derived.

Our analysis of the data in this manner revealed that in these three studies, there were really no substantial changes that resulted, although in numerous instances, a definitive answer could not be arrived at because of the basic inadequacies and improper procedures used in the execution of these studies.

I would like to emphasize the point that we were specifically instructed not to be concerned with, or to comment upon, the overall validity of the study. This was to be done in a subsequent review, carried out at a higher level.

It is apparent that the review, on a point-by-point basis, that was done later discarded or ignored the problems and the deficiencies outlined in this team report and concluded that, even in toto, all of these problems were insufficient to render the study invalid.

It also appears that the serious departures from acceptable toxicological protocols noted in the reevaluations of these studies were also discounted.

At this point it might be helpful to mention some of these deficiencies and improper procedures that were encountered:

(1) There was no protocol written until the study was well underway; (2) Animals were not permanently tagged to avoid mixups over the course of the study; (3) Changes were introduced in some laboratory methods during the study with inadequate documentation; (4) There was either sporadic or inadequate reporting and monitoring of both feed consumption and animal weights; (5) In some cases, tumors were removed, and the animals then returned to the study; (6) Animals were recorded as dead and then subsequent records, after varying periods of time, indicated the same animal was still alive—almost a certain evidence of mixup; (7) Many animal tissues, a significant number, were autolyzed, that is, decomposed, before any post mortem examinations were performed; (8) And finally, of extreme importance is that in the DKP study there was evidence, including pictures found in notebooks at Searle, that the diets were not homogeneous, and that the animals could discriminate between feed and the included particles of DKP. In other words, they may or may not have been eating what it was assumed they were eating.

Almost any single one of these aberrations would suffice to negate a study designed to assess the safety of a food additive, and most certainly, a combination of many such improper practices would, since the results are bound to be compromised.

It is unthinkable that any reputable toxicologist giving a completely objective evaluation of this data resulting from such a study could conclude anything other than that the study was uninterpretable and worthless and should be repeated. This is especially important for an additive such as aspartame, which, as we have heard already today is intended for and is now being used in such a widespread and uncontrolled fashion.

It is equally vital, since this DKP, the subject of the study that I am referring to, is a major breakdown product of aspartame in liquid media.

So what we essentially have is that not only is aspartame being used in the absence of basic toxicity information, but there is also no data to assess the toxicity of interactions of this DKP with excess phenylalanine, with any other metabolite of aspartame, or with interactions of other additives, drugs or other chemicals, which may be simultaneously present in persons exposed to high levels of DKP in pre-sweetened liquids such as diet drinks.

While I have not been involved in safety matters concerning aspartame since this team effort described some time ago, a brief

examination of studies completed and currently underway seems to indicate that the subject studies have not been repeated, so the safety questions, and hence the acceptable daily intake figures that were derived from them remain in question and remain unanswered.

It would appear that the safety of aspartame and its breakdown products has still not been satisfactorily determined, since many of the flaws cited in these three studies were also present in all of the other studies submitted by Searle.

That is the end of my statement, Senator. Thank you.

Senator METZENBAUM. Thank you very much, Dr. Verrett.

Dr. VERRETT. I should say that I also did a literature survey of the NIH/NLM Libraries. I have brought that with me. It is not organized, but I think it might be of some help to you in determining exactly what has been done. In a quick scan of it, I do not find studies that repeat any of this research enough to answer the questions that were raised.

Senator METZENBAUM. So that many of the studies that have been reported subsequently were based upon the findings of the original study, and the original study is the one that you found so flawed?

Dr. VERRETT. That is correct. That sort of applies to some of the discussion that you had recently. Many other countries, in evaluating the data, did not actually evaluate the raw data. They accepted the fact that Food and Drug had found it safe. They did not have the opportunity to look at the raw data and to see the flaws in the basic experiments that were done.

Senator METZENBAUM. Dr. Verrett, you are a Ph.D.?

Dr. VERRETT. Yes. I have a Ph.D. in biochemistry from Fordham University. I have also degrees in physical chemistry as well. My first full-time job, actually, was with Food and Drug. I left there about nine years ago, and I am now employed as a consultant, primarily with EPA.

Senator METZENBAUM. Did you know there were nearly 170 studies submitted to the FDA to prove NutraSweet's safety; of those, 9 were crucial to safety. You reviewed, really, the basic one, the long-term DKP study.

Dr. VERRETT. Yes, that was one of the so-called critical. And the other two——

Senator METZENBAUM. Why is that important? Why is that so important?

Dr. VERRETT. Because it was recognized even then that DKP is formed to a large extent when liquids in particular are presweetened with aspartame. Its production is also very much subject to increases in temperature. And based on the information that was presented at that time—and I think to some extent that has been reinforced—the higher the temperature, the more of this DKP that is formed; in other words, sitting on the shelf, we are getting this compound formed.

And incidentally, in spite of the sweetness of aspartame, because of its decomposition in liquids, I have read that a majority of the diet drinks, and other products of that nature, use somewhat more than would really be necessary for sweetening in order to compensate for this decomposition over a long shelf life.

So it is acknowledged, and that is why initially, aspartame was not intended or not planned to be used in liquids because of this decomposition.

Senator METZENBAUM. The first study that was made—was this at the time that dry substance was being talked about?

Dr. VERRETT. The study that I am talking about?

Senator METZENBAUM. Yes.

Dr. VERRETT. Yes, of course. This was a dry mixture of solid DKP crystals into the animals' diet. This was not a study of it in drinking water or anything like that.

Senator METZENBAUM. There was no mention of taking it in the quantities that it is now ingested in liquid form, so that the original studies were made when it was contemplated that there would be a very limited ingestion of DKP in——

Dr. VERRETT. I am not sure I can answer that accurately, Senator. The thing is that I think it was initially proposed for both uses, but that with the data that were generated on its breakdown to DKP and so forth, that it was decided that it was too unstable to be used in hot preparations, hot liquids, and also in diet drinks. And it was only later that those uses were added. First, the approval in 1974 was strictly for dry foods. Even that, on the basis of what I am describing here, was based on relatively questionable data.

In other words, we really do not know with any degree of certainty, as far as I can see, that this ADI and these other figures we are talking about have any meaning whatsoever, because the quality of these critical studies in which animals were fed these materials for one, two years, and so forth, was such that any kind of calculation of a no-effect level, if you wish, in that study, which is used to develop the ADI, cannot have any degree of accuracy about it. And the problems in this research—and these are not all of them but, I have listed some of the most serious—but the problems in this study were common to all of the studies in some degree. And I should say it leaves a huge question about teratology, birth defects, things that have been discussed by other panelists.

Those two teratology studies that I reviewed, in addition to the DKP that my panel looked at, were also woefully inadequate.

Senator METZENBAUM. Dr. Verrett, let me quote to you from a Searle Company memo dated December 28, 1970. The author was Mr. Helig, and in the memo he talks about their strategy for getting NutraSweet approved: "The basic philosophy of our approach to Food and Drug should be to try to get them to say 'yes', too, even if we have to throw some in that have no significance to us other than putting them into a 'yes'-saying habit. We must create an affirmative atmosphere in our dealing with the FDA. It would also help if we can get them, or get the people involved, to do us any sort of favor, as this would also bring them into a subconscious spirit of participation. My prime concern at this time is with the production of aspartame and our lack of complete toxicological data on DKP."

How do you react to that?

Dr. VERRETT. My first reaction is that I am not at all surprised. I had not been aware of this, of course, before. And I do not want to imply that there was anything dishonest in this submission or others that I have had dealings with. But I have been involved

with a number of the industries, read many of their petitions, and it seems to me that they do use pressure because they themselves maybe are really convinced that there is nothing wrong with these things.

And I have been to many a meeting where that kind of approach which was suggested there was used. It is obvious we were being conned, or put in a mental state of thinking we didn't have a problem, before we ever read the data. Now, I am not saying this was dishonest, either. And this data certainly seemed to be an honest admission. You know, it wasn't manipulated. Certainly, if anybody had tried to make this up, they couldn't have; they would have had to do it better.

So I do feel in my 20-year experience there, to the extent that I had to deal with representatives of industry, many of whom I have a very high regard for, certainly, but that there is a subtle pressure, brainwashing, if you wish, and one does have to go through this sort of data with a fine-toothed comb.

Now, admittedly, some of the procedures that are currently used now were not always used. One of the problems here was that we accepted, not only from Searle but from everybody, summarized data. We had no way of knowing the fact that animals died and were being resurrected, missing, mixed up, all of this, until something called attention to it. And I should say that in this case aspartame was not the only substance that was being investigated at Searle. It happened at that time there were also two drugs for which there were apparent problems, so inspectors went in and, I think, looked over a series of things, one of them, aspartame, being the food additive that was chosen.

But the problem is that even had this study been done perfectly—if there is any such thing—if they had followed the protocol—interpretation of the results would not have been clear-cut. We did not even in that day, need the good laboratory practices; the GLP regulations are helpful, and we tell people exactly what to do now, but any high school pupil or high school teacher with common sense would know that you have to identify your animals individually, otherwise you cannot tell them apart. All white rats look alike. And some of the deficiencies maybe trivial, if you want to say that, on an individual basis; this is exactly the way the investigating committees or whatever they were that examined these studies after my task force did, that is exactly the way they treated them. All of the deficiencies that we pointed out on a one-by-one basis, they quietly said, "Oh, that is not that important of itself," and then they promptly dismissed all 25 or 30 of them in toto, after having said each one was irrelevant.

They even contradicted themselves. This (DKP) is the famous study with the uterine polyps, and it is also the study in which there were changes in serum cholesterol, significant changes over the dose range.

Now, we still are not sure exactly how much of DKP each group of animals or any individual animal got; they may not have gotten what would be calculated on the basis of daily consumption had the diet been homogeneous.

The fact is, in spite of that, there were significant increases—and I think everybody agrees with that—of uterine polyps and also changes in blood cholesterol.

When that was then taken into consideration, they said, oh, well, obviously, they must have gotten the diet, because we have these changes. But then they disregarded the changes as being significant—you know, uterine polyps were not pre-carcinogenic. Well, I can rustle up 15 million women by this afternoon who will disagree with that.

Senator METZENBAUM. Would you say, generally speaking, the whole basis of approving NutraSweet as related to the DKP study that came before you was invalid?

Dr. VERRETT. Not only the DKP study. I feel that some of the other studies of aspartame—I read the others as well, although the memo specified that we analyze the DKP study—and the two studies on teratology,—I feel that as a minimum, they are seriously flawed because of enough problems in the way they were conducted that it makes it difficult to interpret them and come up with any kind of a figure in which we could have confidence for an ADI.

And of course they certainly did nothing to deal with the other issues that have been discussed here today, such as effect of phenylalanine excess on the brain or other neurotoxic effects; these are simply crude, "rough-and-dirty", if you wish, hammer-and-tongs approaches—feed in excess and see what effects you get. There was nothing in them to look at the metabolism, to find out what it was breaking down into. These are just the basic things to try to find out what is the toxic dose to a rat or mouse, and I feel we really do not have that yet with any certainty.

Senator METZENBAUM. As a Ph.D. toxicologist for 20 years in the FDA, and as someone who as examined the scientific validity of this test, apparently, you would totally disagree with the Commissioner's statement that he has complete faith in the credibility of tests used to approve the product.

Dr. VERRETT. I do disagree with that, I am sorry to say.

Senator METZENBAUM. You do disagree.

Dr. VERRETT. Yes, because if it is these studies—and I am limiting my comments on the submission by Searle—I do not feel that they provide us any information, or let us say, they do provide some information, but there are so many problems such as those that I cited in not only this DKP, but in the others as well, that we cannot come up with any assurance that we have the right ADI.

Senator METZENBAUM. You are quoted in a recent UPI story as saying that you just wanted to come out and say that this whole experiment was a disaster and should be discarded. What stopped you? Were you restricted in any way?

Dr. VERRETT. Well, they told us in no uncertain terms that we were not to comment on the validity of it. And I hoped, although having been there at that point for 19 years, I should have known better, that there really would be an objective evaluation of this beyond the evaluation that we did.

I do not feel that that was done, based on what I have read in the GAO report that I have looked at and so forth. They definitely did not objectively evaluate these studies, and I really think it should have been thrown out from day one.

We were looking at a lot of little details and easy parameters in this study, when the foundation of the study, the diet and all of these other things, were worthless. We were talking about the jockey when we should have been talking about the horse, that he had weak legs. It is built on a foundation of sand.

Senator METZENBAUM. Do you think we should repeat the test?

Dr. VERRETT. I feel it, yes, unless—I am unaware of some that have been done, and that were done properly, and would give us some assurance of being able to calculate these values that we need. But I have no qualms in saying that if we are basing the amount of aspartame that we are putting in all of these foods today on these studies, then it is a disaster.

Senator METZENBAUM. Thank you very much, Dr. Verrett. Your testimony has been very helpful.

Dr. VERRETT. Thank you, Senator, for having me testify.