Drug Administration.

As I mentioned previously, Mr. Fred Branding of your office has been kept fully advised of all pertinent developments in this case. Many of the attorneys in our office have had the privilege of working with him in cases recommended by our office. In his conversations with Mr. Levine over the last months, he has expressed a strong interest in this case and we would warmly support his designation as the attorney in your office responsible for reviewing the matter and handling the presentation to the Grand Jury.

As you know, this office cooperates closely with the Consumer Affairs Section in the prosecution of cases under the Act. A copy of this transmittal letter has been sent to Mr. Robert McConachie, Acting Chief. We anticipate that we will be apprised of your review of this transmittal and we and the Consumer Affairs Section will appreciate being kept advised of any developments. Mr. Sharp has already identified many potential witnesses to support the pathology and toxicology principles that underlie the charges in the 305 Notice and the Task Force report.

We look forward to hearing from you following your initial review of these materials, and discussing with you a schedule for future action on this important and precedent-setting case.

Very truly yours,
Richard A. Merrill,
Chief Counsel,
Food and Drug Administration.

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STATEMENT FROM ADRIAN GROSS, FORMER FDA INVESTIGATOR AND SCIENTIST

In the pages to follow here I am presenting a number of comments which you may find informative in any future efforts to curtail exposure to aspartame; those comments are centered around three main topics:

(a) The studies carried out by G.D. Searle & Co. to establish the safety of aspartame are to a large extent unreliable; this is a conclusion that would follow the FDA's own extensive investigations into the acceptability of experimental studies conducted by and for Searle; see top of page 2 here.

(b) Their serious shortcomings notwithstanding, at least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals and that this predisposition of it is of extremely high significance; see bottom of page 16 here.

(c) I would view the Acceptable Daily Intake (ADI) set by the FDA for aspartame (50 mgm/kgm body weight/day) as totally unwarranted and extremely high in that it can be associated with completely unacceptable risks as far as the

induction of such tumors is concerned; see top of page 19 here.

(a) The reliability of studies with experimental animals carried out by and for G.D. Searle & Co.

Beginning at the top of the next page there are given a number of quotes from the Final Report of the FDA's Task Force dated March the 24th, 1976, which had investigated the G.D. Searle & Co.:

It is important to realize that this particular document, although signed by the members of a special Task Force appointed by FDA Commissioner Alexander M. Schmidt, in fact represents an FDA INSTITUTIONAL view. At the Joint Hearings held by the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary of the United States Senate (both Subcommittees then chaired by Sen. Edward M. Kennedy of Massachusetts) on April 8 and 9 and July 10, 1976, Commissioner Schmidt said (page 3 of the record of that hearing): "today I would like to report to you the FINAL RESULTS OF THE FOOD AND DRUG ADMINISTRATION'S (FDA) DETAILED INVESTIGATION of animal studies performed by Searle...." (emphasis added).

(Page 4 of the record of that hearing):

"Senator Kennedy. Let me ask you this. These are the conclusions of the (Task Force appointed to that) study. Do you agree with those conclusions?"

"Dr. Schmidt. Yes, I do."

"Senator Kennedy. Yes, you do. Is this the first time, to your knowledge, that such a problem has been uncovered of this magnitude by the Food and Drug Administration?"

"Dr. Schmidt. It is certainly the first time that such an extensive and detailed examination of this kind has taken place. We have never before conducted such an examination as we did at Searle."

"From time to time, we have been aware of isolated problems, but we were not aware of the extent of the problem in one pharmaceutical house ..."

I have reproduced here that particular exchange verbatim since in recent years and apparently at the urging of G.D. Searle & Co., Dr. Schmidt has found it expedient to distance himself from the conclusions in that particular report which he had accepted and represented as his own and as those of the agency he headed at the time (see the copy of the affidavit that he swore to on February the 4th, 1983, and the one sworn to by me subsequent to that date, both of which I had given to you).

To quote then from that particular report of the Task Force identified at the top of this page, much of which was also quoted by Commissioner Schmidt himself

at the Senate subcommittee hearings mentioned above here:

(Pages 1 and 2 there):

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

"Reliance on a sponsor is justified when FDA has reasonable assurance that the sponsor will: (1) inform the agency of ALL material results, observations, and conclusions of an experiment, (2) report fully and completely ALL of the conditions and circumstances under which an experiment was conducted, and (3) submit its reports to the FDA in a timely fashion so that measures to protect the public health and safety can be taken promptly when warranted. Through our efforts, we have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products."

"Searle has not met the above criteria on a number of occasions and in a number of ways. 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. Some of our findings suggest an attitude of disregard for FDA's mission of protection of the public health by selectively reporting the results of studies in a manner which allays the concerns of questions of an FDA reviewer. 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."

"Unreliability in Searle's animal research does not imply, however, that its animal studies have provided no useful information on the safety of its products. Poorly controlled experiments containing random errors blur the differences between treated and control animals and increase the difficulty of discriminating between the two populations to detect a product induced effect. A positive finding of toxicity in the test animals in a poorly controlled study provides a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that the results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product."

In addition to these general comments which are meant to apply to any study with experimental animals conducted by G.D. Searle & Co., that same Task Force Report contains additional references to problems encounteredfor individual studies carried out by G.D. Searle & Co. SPECIFICALLY for aspartame:

(Page 25, paragraph 3): "In the Aspartame (DKP) 115 week rat study, the submission (to the FDA) states that twelve lots of the test compound, diketopiperazine, a metabolite of Aspartame, were manufactured by a Searle chemist and used in the study. However, the investigators found that some of the batch numbers were merely different drum numbers and actually only seven batches were made. Searle personnel informed the investigators that records of manufacture and assay of two batches could not be located."

(Page 26, last paragraph): "Significant deviations from the protocols of several studies were noted which may have compromised the value of these studies, including the excision of tissue masses (which are likely to represent mammary tumors) from live animals during the course of a study. There is no indication that these deviations were reviewed or approved by the Protocol Design Committee; hence they may represent serious unauthorized changes in the experiments. ... In at least one study, the Aspartame 52 weeks monkey study, the protocol was written AFTER the study had been initiated."

(Page 31, paragraph 2): "In addition, we found evidence that, as far back as 1969, top management (at G.D. Searle & Co.) concerned itself with the animal studies to determine the safety of its artificial sweetener, Aspartame. An internal strategy memorandum from the Regulatory Affairs Department to top management advises management of tactics designed to produce favorable action by FDA officials and concludes that Searle must get Aspartame into commercial channels as soon as possible to mimimize the incentives of other firms to develop other sweeteners." (actually, the contents of that "strategy" memorandum originating at G.D. Searle & Co. are a veritable eye-opener; I would strongly urge you to actually read it in its entirety if you wish to obtain a whiff of exactly how G.D. Searle & Co. understand to approach their responsibility in the area of assuring the safety of their own products. I was given to understand that the memorandum to which reference is made here was included in the material sent to your Office by the Food and Drug Administration.)

(Page 32, last paragraph): "... there was little continuity of technicians that performed antemortem observations on animals from one observation period to another. In addition to a lack of continuity, there was a lack of adequate supervision and training of the technicians in all phases of the studies, which is documented in the ... Aspartame (DKP) 115 week rat, and Aspartame 42 week hamster investigation reports. ..."

(Page 33, paragraph 2): "In each study investigated, poor practices, inaccuracies, and discrepancies were noted in the antemortem phases which could compromise the study."

(Page 33, paragraph 3): "Protocols normally specified age and sex requirements of animals. In general, these criteria were followed. However, exceptions were found in the 106 week dog study of Aspartame, where the protocol called for dogs to be 150 to 160 days of age and yet three dogs were used in this study that were approximately 70 days older than the protocol specified.

(Page 34, paragraph 2): "At Hazleton Laboratories rats and mice were said to be held for a two week period before they are entered into a study. In the 104 week rat studies of Aldactone and Aspartame there were deviations from this holding period when rats were introduced into the studies after only five or six days respectively."

(Page 36, paragraph 3): "One of the most elementary considerations in a toxicological study is to assure that the test animals receive the active ingredient under test. When the substance to be tested is incorporated into the feed, its homogeneity and concentration in the diet mix should be determined prior to the start of the study. Random samples from freshly mixed batches should be analyzed periodically during the course of the study to ensure that the proper mixing and formulating procedures are being used. In studies conducted by both Searle and Hazleton, little concern was evidenced for the need of proper quality control of homogeneity, concentration, or stability of the active ingredient-diet mixture."

"When Dr. Frederick Reno of Hazleton Labs was asked why Hazleton did not conduct tests on the purity of the test substance, he replied that Hazleton's policy is that the purity of the test material is assumed to be 100% unless notified to the contrary by the client. Tests for (chemical) stability, (biologic) potency and homogeneity of the treatment feed mixture are performed only at the client's specific request; Searle never made such a request of Hazleton in its protocols. Further, Dr. Reno stated that Seale never requested that the basal feed be assayed for residual drugs, pesticides and other contaminants. Hazleton did not conduct such tests for Searle nor were any reserve samples of the treatment mixtures maintained for studies performed for Searle."

"It was noted in the investigation of the Aspartame (DKP) 115 week rat study that drums of the product for each dosage level were identified with color coded labels to match the color of the identification card on the animal cages. When the animal rooms at Searle were inspected on October 17, 1975, it was noted that each drum contained several labels pasted over one another and that the labels underneath the current labels were of various colors. If the current label were to come off, the technician could easily be misled by the label underneath (thus) resulting in a feed mix-up. This is the only study where we found evidence of a test of stability of the test substance in the diet mixture, but the value of this test was negated when, during the course of the study, there was a change in the supplier of the diet and new stability tests were not performed on the new diet-test substance mixture."

"In preparing mixtures of active substance with food both Hazleton and Searle

used blenders that were not electrically grounded. This is of concern because of the potential for the electrostatic properties of the test substance to cause it to adhere to the metal walls of the mixer and/or to distribute unevenly through the food, thereby preventing a homogeneous food-test substance mixture."

"In view of the problems noted with all stages from the receipt of the test substance, preparation of the feed-test substance mixture, the failure of both Searle and Hazleton to analyze for concentration, homogeneity, and stability of the test substance in the diets, and the practices of feed replenishment, there is NO way in which it can be assured that animals received the intended dosage."

(Page 39, paragraph 1): "... investigators toured the animal facilities on October 17, 1975, and noted the following poor current practices at that time: -- "

"An exterminator company is employed by Searle for general pest control in the animal rooms. This company has a blanket order to spray the animal rooms twice a month and additional instructions may be given for specific animal rooms as required."

"The investigators were informed that animals are not removed from the animal rooms during the time that they are being fogged with insecticides. Evidence indicates that this practice has been in effect at least since 1970. A memorandum dated September 25, 1970, from Dr. McConnell to Dr. Victor Drill, which appears as a General Exhibit to the Aspartame inspection report, indicates that Dr. McConnell was concerned about this practice; at the time, however, there was no evidence that this practice was ever discontinued."

"The investigators inquired whether basal diets or treatment mixtures were subjected to analysis for pesticides. No records were found to indicate that any treatment mixtures used in the studies were ever tested or assayed for pesticide content."

"Currently a mixer with a capacity of 10 to 12 kg. is used for blending treatment mixtures. The investigators were informed that the mixture is cleaned with water, alcohol, ether, or is dry cleaned, depending on the material blended. When the mixer was examined on October 17, 1975, however, it was encrusted with material from previous use."

"Records are not maintained of weighing and blending of treatment mixtures. After mixing, the mixtures are placed in plastic, teflon lined containers and are identified with color coded stickers... When the investigators examined the containers on October 17, 1975, they noted that the identification stickers of different colors were present underneath the current stickers and that the edges of some of the top stickers were raised."

"Running inventory records for either treatment mixtures or the test compounds used in treatment mixtures are not maintained. Dr. K.S. Rao, Senior Research Investigator (Toxicology), indicated that it is not necessary to

maintain such records as fresh treatment mixtures are prepared weeky, biweekly, or every four weeks. Clearly, the lack of inventory records, the lack of batch records, and the lack of homogeneity and stability assays, results in poor control over the treatment mixtures."

"The practices enumerated above are such that any or all of them could compromise the integrity of a study."

(Page 42, paragraph 1): "Technicians participated in many studies simultaneously. The technicians weighing, withdrawing blood, feeding and observing the animals for tissue masses, etc., were not assigned to a particular study, but performed those functions for various studies in progress (at one time). . . ."

"Technician Bartolome Tangonen stated that the appearance of his initials at the top of a page (on the sheets entitled 'Observation for Drug Effects' where the heading provides a space for the name of the technician, but which was not invariably filled in) did not necessarily mean that he actually made the observations described in the sheets or that he filled out the sheets which bear his initials. His initials could indicate that he was supervising the work of other technicians or that he was making the observations."

"Numerous errors and inconsistencies were noted in all the antemortem phases of these experiments... Because many of the observations required are of a subjective nature, continuity of the persons assigned to make these observations is critical, yet the names of the observers entered on the same animal groups are often different for subsequent observations."

"Inconsistencies were noted in observations of findings during the course of the Aldactone 78 week study with animals being reported as alive when they were actually dead, and in the reporting of the presence and location of certian tissue masses. These include approximtely 20 instances of animals reported as dead and then reported as having vital signs normal again at subsequent observation periods. (See Attachment 10)."

"Similar inconsistencies are contained in the Flagyl 80 week rat study, the Cu-7 rat study, the Aspartame (DKP) 155 week rat study, and in the Aspartame 46 week hamster study."

(Page 47 penultimate paragraph); "In the supplementary Statement of Mr. Daniel C. Searle dated February 13, 1976, which was appended to the record of the Joint Hearing before Senator Kennedy held on January 20, 1976, Mr. Searle, referring to the errors on Observations for Drug Effects sheets, stated 'In the truest sense, the errors identified by the FDA (in these records) were completely irrelevant to the scientific conclusions of the study...'".

His comment on the irrelevancy of the mistakes on these records relates to his testimony that other records with information as to the date of death and tissue masses were kept by Searle and these other records contained the

'correct' information."

"We do not agree with Mr. Searle that the information on the Observations for Drug Effects sheets is irrelevant."

"The title printed on these 'Observations for Drug Effects' forms is 'Statistical Work Sheet'; it is therefore reasonable to expect that these 'careless' entries must have formed the basis for input for statistical operations which are crucial to the 'scientific conclusions of the study.' ... If the alive/dead status of each animal was 'carelessly' entered on these 'statistical Work Sheets', as conceded by Mr. Searle, and if its status as a tumor-bearer at any time was largely in doubt, as demonstrated here, the statistical computations based on this kind of raw input data are of qustionable value, if any, and would clearly affect what Mr. Searle denominates as the 'scientific conclusions of the study'."

(Page 51, paragraph 1): "In the Aldactone 78 week rat study, the 115 week rat study of Aspartame, and in the Ovulen 7 year dog study, tissue masses (likely to be tumors) were excised from live animals during the course of the study and the animals were continued on the study."

(Page 52, paragraph 1): "The removal of tissue masses from rats in a chronic toxicity study is an unacceptable practice, since it may seriously prejudice the findings of the experiment. For example, if the removed mass, when excised, is found to be BENIGN, ... its excision may have prevented it from becoming malignant, a change which is not unusual, and which is normally a function of time. The purpose of a safety study in animals is to find out as completely as possible ALL the likely risks associated with the test products. Interference with the natural development of tumors will prejudice the findings of the experiment..."

(Page 52, last paragraph): "Animals found dead during the course of a study should be necropsied (examined post-mortem) promptly; when prompt necropsy is not possible, the animal remains should be refrigerated until the next working day, when the post-mortem examination must be performed. Delay or improper handling of dead animals results in the loss of valuable information through autolysis (post-mortem degeneration or spoilage) of tissues. Proper practice following necropsy is to fix (embalm) the tissue in freshly prepared neutral buffered formalin (solution) after slicing the organs and opening the respiratory and digestive tracts to permit penetration of the fixative to prevent autolysis."

"In a number of studies which we investigated at both Searle and Hazleton, loss of information through autolysis of tissues was substantial. While Searle's (written) submissions to FDA stated that animals were necropsied promptly after death, FDA investigators found that this was not always true; frequently animals were fixed in-toto (i.e., without opening up the various organ systems tracts and dissecting and slicing of organs) after opening only the thoracic and abdominal cavities and holding them for periods sometimes longer than a year

before they were necropsied. Fixation in-toto is an unacceptable practice and its use by Searle had to contribute to tissue loss. At Hazleton, there was no evidence of fixation in-toto. However the unacceptably high incidence of autolysis, 14 percent in one study, indicates improper handling of the tissues."

"In the Aspartame (DKP) 115 week rat study at Searle 98 of the 196 (50 percent) animals that died during the study were fixed in-toto for periods ranging from 1 day to 1 year before they were necropsied. Of these, 20 animals had to be excluded from postmortem examinations because of excessive autolysis. Dr. K.S. Rao (of G.D. Searle & Co.) realized that Searle's procedures with regards to delays in necropsies were not proper. In a memorandum to Dr. McConnell dated July 13, 1973, Rao stated: "I realize animals which die during the study are the most critical ones to evaluate the (test) compound effects. Hence, our people are now ready to perform a complete autopsy of the dead animals. If there are any special instructions in handling the brain and spinal cord, please advise." (Exhibit R-64 to the Aspartame 115 week rat study). However, Dr. Rao did not write this memorandum until 78 weeks into this study (i.e., not until more than half of the time devoted to it has elapsed). Of the 20 animals in this study which had to be discarded because of excessive autolysis, 13 died prior to Dr. Rao's memorandum; the remaining 7 died subsequent to that memorandum, indicating that his recommendation for prompt necropsy was not followed. In fact, Searle's records show that only 3 of the 20 animals were necropsied on the day they were found dead. Similarly, in the ... Aspartame 46 week hamster studies, a number of animals that died were fixed in-toto and necropsied at a later date."

(Page 55 at the top): "Searle had no formal training program for its prosectors (the technicians actually carrying out necropsies or gross post-mortem examinations of the carcasses and tissues of the experimental animals); its on-the-job training was minimal. An example of this is shown in the Aspartame (DKP) 115 week rat study where the necropsy of the animals was performed by Mr. Spaet. His written observations of gross pathology were later changed by Dr. Rudolph Stejskal, who was (designated as) the supervising pathologist on this study but who was NOT physically present during these autopsies (and, consequently, could not have verified the presence, absence or extent of the lesions observed and recorded by Mr. Spaet). When questioned by the investigators as to why he made these changes, Dr. Stejskal stated that Mr. Spaet was employed for only a few months and was encouraged to write down everything that appeared to be questionable or unusual. He also informed the investigators that Mr. Spaet sometimes used wrong terms in the description of his findings. The gross pathology observations submitted in the Food Additive Petition (to the FDA) were selected by Dr. Stejskal and represented his interpretation of Spaet's observations. Dr. Stejskal indicated if he could not confirm a gross observation microscopically, he would then omit the gross observation from his report. (Actually, failure to confirm a gross observation microscopically may not be due to the usage of a wrong term but simply due to a failure to collect for microscopic examination a representative part of a lesion actually present; therefore, what Dr. Stejskal may have very likely achieved here was to withhold from the attention of the FDA possibly real lesions in

those experimental animals in which Aspartame was tested for safety.) ... Had a professional (pathologist) been available to confirm Spaet's findings directly or to provide him with a practical on-the-job training during necropsies, then it would not have been necessary for Dr. Stejskal to have to change (perhaps improperly) or 'second-guess' Spaet's observations. Moreover, Mr. David Kie, a more experienced prosector, was also available during these necropsies and did some of the prosecting himself. Review of the gross pathology records disclosed that, in at least one instance, Dr. Stejskal omitted a statement made on the gross observation sheet by Mr. Kie."

(Page 57, paragraph 2): "Histopathology (the lesions manifest in any tissue by examination under the microscope) is an extremely important morphological indicator of the effects of an insult upon a tissue or cell. Careful preparation, cutting, slicing, mounting, staining, and interpretation of histologic slides from animal tissues to determine the changes occuring in test animals during the course of, and to some extent, as a result of the administration of a test substance to the animals, is crucial if the investigator is to glean valuable information from the experiment. Much valuable histopathologic information was lost in some of the studies which we investigated at Searle and Hazleton through preparation of poor quality slides which could not be interpreted by pathologists; inadequate numbers of acceptable quality slides of certain tissues upon which conclusions were based; and violations of protocol specifications which called for slides to be made of certain tissues for histopathological evaluation which was not done."

"In the Aspartame (DKP) 115 week rat study at Hazleton 3 tissues were noted on single animal sheets as having usual or unusual lesions and, yet, contrary to the protocol, slides were not prepared of this tissue for microscopic examinations. ..."

(Page 60, paragraph 3): "Included in the report (by G.D. Searle & Co.) to FDA of the Aspartame hamster study is the report (of findings following examination of the) slides of several organs of one animal for which our investigators determined that slides were never prepared... In the Aspartame 104 week rat study conducted at Hazleton, 5 animals were described as having tumors in the histopathological incidence table. A check of the slides and blocks (of tissue from which such slides must have been prepared) reveals that neither were present for the tissues in which the observations were made. Also at Hazleton, positive findings were reported by pathologists on 15 slides of this study but no record could be found that slides were ever made of these tissues. Since the investigation, Hazleton has attempted to determine the source of these errors relating to the tumor slides. The Task Force has received no report of Hazleton's findings."

"Part of the difficulty in attempting to identify precisely what tissues have been examined and what tissues have been reported to the FDA and to make a reasonable assessment of what happened in the conduct of the study, results from the lack of "original" postmortem work sheets or documents. Such instances include the Aspartame 115 week and 104 week rate studies; ..."

"An example of one occurence which demonstrates the inadequacy of control between gross pathology and histopathology at Searle is available in a description of animal K23CF (an unexposed female animal) in the 115 Aspartame (DKP) rat study. This animal, a control female, was reported on gross necropsy as having a tissue mass of approximately 10x8x3 cm in the left inguinal region. A notation, in a different handwriting, made at the bottom of this gross observation records states, 'no (tissue) mass found in bottle (of fixative into which specimens of such tissue masses are to be placed so as to enable one to collect a sample of such masses for microscopic examination and characterization as to the nature of the mass)'. In the microscopic findings of this study the mammary gland is reported as having a 'necrotizingcystadenocarcinoma (a MALIGNANT tumor of the mammary gland); well differentiated.' Dr. Stejskal (the pathologist at G.D. Searle responsible for the pathology operations on this particular study) was asked how it would be possible for this mass to have been read microscopically when the technician responsible for preparing the slides indicated that the mass was not contained in the specimen bottle. (Note that by pretending that a control or unexposed animal manifested a malignant mammary tumor when in fact that animal did not have such tumor or even if it did, that tumor could not be found and therefore could not be confirmed to be a mammary gland cystadenocarcinoma, the significance of the incidence of such tumors amongst animals exposed to Aspartame has been improperly reduced). The pathologists's (Dr. Stejskal's) response, as reported by the investigators, was that, at the time the animals were sacrificed (i.e., killed so that their tissues could be dissected and examined) 'you should have seen things when this study was run -- there were five studies being run at one time -- things were a mess'."

(Page 62, paragraph 2): "Because of the serious consequences of teratogenicity (the ability of an agent on test to elicit developmental or birth anomalies in the newborn), assessment of the potential of a test substance on reproductive and developmental processes constitutes an extremely important phase in safety evaluation. The rapid rate of change in morphological, biochemical and physiological properties of the conceptus, the embryo, and the neonate presents special problems. Important considerations are selection of appropriate species, and absorption of test substance. The planning, performance and evaluation in this sphere requires a high degree of sophistication."

"The person responsible for most of the reproduction studies reviewed was apparently inexperienced in conducting studies of this nature and yet was given full responsibility at Searle with a title of Senior Research Assistant in teratology. His prior experience was one year's employment with the Illinios Wildlife Service where his work involved population dynamics of the cotton tail rabbit. When asked by the investigators during an interview what qualifications or training he had for conducting reproduction and teratology studies, he replied that shortly after his employment (began at Searle) he went to a meeting (lasting at most for a few days) 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."

(Page 64 paragraph 3): "Review of 5 reproduction and teratology studies for Aspartame revealed poor animal husbandry practices and problems in the design of some of the studies. In a memorandum of October 19, 1972, from a Searle technician to Dr. Rao, with copies to his superior and to Dr. McConnell (of Searle), regarding the conception rate in the rabbit teratology study PT 1044S72, the author provided some possible reasons for the observed poor conception rate in the remaining animals following the death of 13 animals in this study. The memorandum includes statements regarding the poor physical condition of the animals when they were received by Searle, e.g., diarrhea; the lack of an adequate acclimatization period, e.g., 6 days instead of 3 weeks; breeding the animals before they were sexually mature,e.g., insemination at 96-116 days instead of 160-240 days and pseudopregnancies because of injection of hormone. The memorandum concludes with this paragraph:

"'In view of the information that I have received, I feel the majority of the animals used for this study were sexually immature. Pseudopregnancy of some of the 27 rabbits may have also contributed to the lower conception rate. Some of these points were discussed at the beginning of this study, however we decided to go ahead as scheduled. Perhaps this information can be utilized in future teratology studies so that this type of problem will be eliminated.'

"A July 15, 1975, letter to Searle from one of its consultants on reproduction and teratology (Dr. Geoffrey Palmer from Great Britain) commented on the quality of the studies as follows: '... even following the track you did, it seems to me you have only confounded the issue by a series of studies most of which have severe design deficiencies or obvious lack of expertise in animal management. Because of the(se) twin factors, all the careful and detailed examination of fetuses, all the writing, summarization and resummarization is of little avail because of the shaky foundation.'"

(Page 66, paragraph 1): "... We conclude that Searle rarely monitored the performance of work done for it under contract (by other laboratories or institutions)."

(Page 66, paragraph 3): "Searle characterized the 52 week monkey study (with aspartame) by Dr. Waisman at the University of Wisconsin as a first priority with the Searle Company. Yet, to the investigators, Searle disclaimed any direct control in the study, despite the facts that the protocol (detailed specifications on precisely how the study is to be carried out) for the study was written by Dr. McConnell (of G.D. Searle & Co.) AFTER Dr. Waisman initiated the study in January 1970; that frequent high-level communication took place between Searle executives and Dr. Waisman prior to and during the study; that Dr. Waisman was paid $15,000 by Searle for consultation on Aspartame; and that Searle provided Dr. Waisman with 200 grams of Aspartame to conduct the studies."

"While high-level communication between Searle management and Dr. Waisman, and knowledge of his activities (Waisman gave a seminar at Searle on his work in

October 1970), is evident, there was virtually no effective monitoring of this work."

"From what can be inferred from an interview with Dr. McConnell on October 14, 1975, he had serious reservations about the quality of the study, but he then went on to indicate that, in the absence of hard data to substantiate his reservations, there was no way to set them down in written form in a submission to FDA (i.e., he gave no indication whatsoever to the FDA on such reservations as he said he had)."

(Page 80 at the top): "In the Aspartame 46 weeks hamster study, blood samples reported in the submission to FDA as 26 week values (for certain specified animals) were found by our investigators as being, in fact, values for different animals which were bled at the 38th week. Many of the animals for which these values were reported (to the FDA) were dead at the 38th week."

"In attempting to understand the entries in Table 8 of the Aspartame Food Additive Petition (submitted to the FDA by G.D. Searle & Co.) which described clinical chemistry values (Exhibit H-14 to the inspection report of the 46 week hamster study), the investigators interviewed Dr. K.S. Rao (of the G.D. Searle & Co.) on November 11, 1975, and asked him to clarify certain BUN (Blood Urea Nitrogen) values found in that table. After reviewing the table from the submission (to the FDA) and the original data (in G.D. Searle's own records of observations from which allegedly what was reported to the FDA originated), Dr. Rao replied in writing stating:

"'It is apparent from the report, that the Appendix portion contains all the individual (animal) values of clinical lab data available from the raw data file. A selected portion of these values appears to have been used in computing group means (which were reported to the FDA). It is not clear what criteria may have been used for selecting a portion of the data or for deleting the others in computing the means (reported to the FDA).'

"'For the above reasons, I cannot compute the means for the BUN values indicated (in the report submitted by G.D. Searle & Co. to the FDA) from the data available in the Appendix portion of the report.'"

"In the Aspartame 115 week rat study, the investigators point out data appearing on two tables, one in the raw data (in Searle's own files) and the other in the submission (by G.D. Searle & Co.) to the FDA. It is impossible to determine how some of the values in the submission were arrived at, although in two instances the submitted values appear to be an average of the two values shown in the raw data, and in other cases, it appears that a single value was selected from the two values which appear in raw data. These findings appear on pages 10 and 11 of the inspection report of this study and in Exhibits R34 and R35."

Following these quotations from the Final Report of the Searle Task Force, it may be useful to relate here what happened in the Fall of 1975 following that

investigation at G.D. Searle & Co., particularly in reference to the aspartame studies:

Inasmuch as only a very small fraction of the fairly large number of studies on aspartame carried out either by or for G.D. Searle & Co. could be audited by the investigators at that time, the decision was made by the FDA to have the original records maintained by G.D. Searle & Co. for the balance of those studies sealed in place at G.D. Searle & Co. so as to preserve their authenticity for a future date when they might also be audited.

In fact, however, the only additional audit as far as aspartame studies are concerned that was carried out by the FDA did not take place until April to August 1977, i.e., almost TWO YEARS subsequent to the original audit. Even then, only three additional studies were audited: two of these were relatively minor ones on the embryotoxic and teratogenic potential for aspartame (one in the rat and one in the mouse) while the third one was the same long-term study in rats of 115 weeks with DKP that had already been investigated during the original audit in 1975. Aside from this, as far as I know, no additional efforts at auditing any other study on aspartame was made by the FDA despite the fact, as mentioned earlier, that a relatively very large number of studies with experimental animals have been conducted by or for G.D. Searle & Co. for this particular food additive.

This apparent refusal by the FDA to do what would have been the "right" thing to do in this case is even more difficult to comprehend if one considers additionally that.

In December 1975 i.e., as a consequence of the initial findings by the FDA on the reliability of the aspartame studies conducted by and/or for G.D. Searle & Co., the FDA decided to prevent aspartame from entering the market;

The findings during the 1977 audits not only confirmed those made in 1975 with respect to the lack of reliability of the studies of aspartame, but actually extended them in a substantial fashion;

Despite all this, the FDA refused to allow its findings on the reliability of the aspartame studies to be put before the Scientific Board of Inquiry concerning aspartame which had been convened following the request of Dr. John W. Olney of the Washington University School of Medicine in St. Louis, Mo. and Mr. James Turner, a Washington, DC attorney. This refusal took place even though the two gentlemen insisted that such concerns on the reliability of the two studies were directly related to the evidence (or lack of it) for the safety of aspartame;

Although largely as a result of the findings arising from the 1975 investigation at G.D. Searle & Co., the U.S. Congress appropriated an additional $16,000,000 or so to the FDA for the express purpose to do a better job at monitoring the quality of studies carried out by the regulated industry and although the FDA took this money and recruited a large number of investigators

ALLEGEDLY TO DEVOTE TO THIS PROGRAM, other than the limited audits carried out in 1977 by the FDA with respect to aspartame, apparently nothing more in the way of such audits were carried out for this particular product. Therefore, most of the raw data that had originally been sealed by the FDA at G.D. Searle & Co. in 1975 were eventually unsealed and returned to the custody of G.D. Searle & Co., without any further attempts at validating the reliability of such reports as that firm had elected to submit to the FDA on the safety of aspartame.

This kind of track record on the part of the FDA does not seem to me to inspire much confidence that the health of the people of this country is in fact adequately protected by its regulatory activities.

As to what was uncovered as a result of the 1977 audit, you may recall that I had given you a copy of that particular EIR (Establishment Inspection Report); that 76-page document came to be known as the "Bressler Report" after the name of the leader of the team of investigators and scientists that participated in that particular audit, Mr. Jerome Bressler, an FDA investigator located in the Chicago District. A perusal of its contents reveals that the original (1975) findings with respect to the 115-week rat study with DKP, or diketopiperazine, a breakdown product of aspartame, were confirmed with respect to:

Discrepancies between what was found in G.D. Searle's own internal records on the circumstances of the conduct of this study and on the observational findings actually made and what was actually reported by that firm to the FDA with respect to:

-- The presence of tissue masses likely to be tumors (e.g., animal No. F6HF;

-- Grossly detected pathological changes in general for the experimental animals;

-- Records of ophthalmoscopic examinations for those animals;

-- The alive/dead status of each animal at any given time;

-- The presence of certain microscopically evident lesions when the G.D. Searle & Co. records indicate that such findings could not possibly have been made since no such examinations were made;

-- Problems with clinical laboratory determinations;

The multifaceted evidence for this study being flawed due to:

-- Substitution of some of the animals in the study;

-- The presence of intercurrent disease and the administration of drugs to combat this, neither of which were completely reported to the FDA;

-- Incomplete examination of tissues from the experimental rats;

-- Excision of tissue masses likely to be tumors from live animals in this study;

-- Absence of batch records and records for the mixing of the test substance into the diet of the experimental animals;

-- Incomplete stability studies for the agent on test;

-- Absence of homogeneity studies for the agent on test;

-- Deficiencies in the methods of chemical assay for the actual DKP that was mixed into the diet of the experimental rats;

-- Problems with the dosage of DKP given to the experimental rats;

-- Problems with the fixation in-toto and autolysis;

-- Failure to report to the FDA of all tissue masses (likely to be tumors) which were found in the experimental rats;

-- Failure to report to the FDA of all internal tumors present in the experimental rats, e.g., polyps in the uterus (Animal K9MF, ovarian neoplasms (Animals H10CF, H19CF, and H7HF) as well as other lesions (Animal D29CF);

-- Inconsistencies between different parts of the report on this study submnitted by G.D. Searle & Co. to the FDA on the percise nature of the lesions manifested by the test rats;

-- Numerous transcription errors in that report.

Interestingly, the Bressler group found not only that no homogeneity tests were conducted by G.D. Searle & Co. on the mixture of the test agent with the diet of the experimental rats, but they obtaned direct evidence that in fact the distrbution of the test agent in that diet was clearly not homogeneous due to failure to have the test agent ground in a sufficiently fine manner. A Polaroid photograph of a sample of that diet obtained by the investigative team actually shows the test agent in the form of coarse particles within the diet. It follows that the experimental rats could eat that diet without actually touching the DKP and, consequently, no-one could state with any assurance just how much DKP (if any) those rats were actually exposed to in the course of that study.

In sum, problems such as this leave rather gaping holes in the reliability of such tests of safety as were conducted by G.D. Searle & Co. not only in general with respect to any of their products, but more specifically with respect to aspartame itself. And yet, it seems as if none of this had inhibited in any way or restrained the FDA from approving this product for marketing in an extremely widespread fashion.

(b) The problem with the brain tumors noted in the experimental animals:

You may recall that amongst the material that I had given you there was a rather extensive prepared statement by Dr. Olney before the Scientific Board of Inquiry. I shall not comment here on the bulk of Dr. Olney's concerns on the safety of aspartame; rather I shall limit myself here to only one aspect discussed by him there -- the matter of the tumors of the central nervous system of the exposed rats. This can be found in Part III of that prepared address of Dr. Olney's.

Table 1 of Part III in that presentation by Dr. Olney presents the pertinent data on this: -- no animals with any brain tumors were noted amongst the 120 control or unexposed rats, 5 were found with brain tumors amongst the 160 rats exposed at the low level of aspartame (1-2 grams/kg. body weight) and 7 were found with brain tumors amongst the 160 animals exposed to the high rate of 4-8 grams/kg. body weight. These three rates represent incidences of respectively 0.00%, 3.13% and 4.38%.

The question that arises as soon as a distribution such as this is observed is quite simple: -- did the agent on test, aspartame in this case, CAUSE the brain tumors noted amongst the animals exposed to it, or rather can one view the occurence of such tumors only in the two groups of rats exposed to aspartame as merely a "chance" event, an occurence unrelated to their exposure status?

The usual way the FDA (and any other recognized scientific institution) answers this kind of question is to compute the probability that a distribution such as the one observed here can arise due to sheer chance; if it turns out that such probability is rather small (0.05 or 5%) the policy in scientific circles is to state that the result observed has achieved "high statistical significance". What this implies is that the probability of the incidences observed arising by chance alone (i.e., that they are UNRELATED to the agent on test) is so small (5% or less) that one would NOT be justified in concluding that the test agent was NOT a factor causing such incidences.

In other words whenever the results of an appropriate statistical test for significance yields a p (for probability) value equal to or less than 0.5 or 5%, THE POLICY IN THE FDA AND IN ANY OTHER SCIENTIFIC OR REGULATORY CIRCLES is to regard the agent on test as being a CAUSE of the increase in incidence of whatever kind of lesion is being evaluated amongst the exposed animals by comparison with the control incidence. I am saying, therefore, that whether the agent on test had in fact CAUSED that particular increase in incidence is not a matter that is usually decided according the "opinion" of any scientist or group of scientists; it is not a matter that is put to some kind of "vote", or on which there must be some form of "consensus"; rather, the decision is made by the results of the test for statistical significance -- the "p" value is either larger than 0.05 and one then views the results as NOT having achieved statistical significance, or it is 0.05 or less in which case one must conclude that the results ARE statistically significant i.e., that they are extremely unlikely to be due to chance alone.

The data on brain tumors amongst the rats exposed to aspartame that were presented by Dr. Olney in his Part III, Table 1, have been analyzed statistically by me and the following are the results of my computations:

Slope of dose-response function	0.005,891
Standard error of this slope	0.003,046
Chi square for significance of this slope	3.724
"p" or probability of this chi square	0.027

The entry in the last row above, $p = 0.027$, indicates that the results on the incidence of brain tumors that were tabulated by Dr. Olney, had in fact achieved rather high statistical significance since $p = 0.027$ is barely more than half $p = 0.05$.

In fact, the statistical significance that applies here is considerably larger yet if one considers that brain tumors amongst rats are ordinarily very rare. In his Table 2 of Part III, Dr. Olney presents the results of what he had gleaned from the world literature on this subject -- the "historical control rate" for such tumors amongst large populations of rats indicates that no more than 49 animals afflicted with them have been found amongst nearly 60,000 rats, an incidence rate of less than one tenth of 1 percent.

Interestingly, the FDA seems to have a policy that whenever faced with decisions of this sort, it never fails to consider this aspect of the "historical control" incidence; a recent example of this can be given in their decision concerning the carcinogenicity or cancer-induction propensities of a number of color additives, a matter that arose as recently as last year. One cannot help wondering just why they failed to consider this particular aspect in reference to the cancer-induction of aspartame. Had they in fact addressed the "historical incidence" of brain tumors amongst rats as presented by Dr. Olney, they could not have failed to conclude what I have concluded: -- that the significance that attaches to those tumors amongst the rats exposed to aspartame increases many-fold over the already high significance mentioned above when what was observed merely in this particular study is considered.

In view of all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask: -- What is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act? Is it not clear beyond any shadow of a doubt that aspartame had caused brain tumors or brain cancer in animals, and is this not sufficient to satisfy the provisions of that particular section of the law?

Given that this is so (and I cannot see any kind of tenable argument opposing the view that aspartame causes cancer) how would the FDA justify its position that it views a certain amount of aspartame (50 mgm/kgm body-weight) as

consituting an ADI (Allowable Daily Intake) or "safe" level of it? Is that position in effect not equivalent to setting a "tolerance" for this food additive and thus a violation of that law? And if the FDA itself elects to violate the law, who is left to protect the health of the public?

(c) Precisely how safe is the FDA's estimate of the Allowable Daily Intake (ADI) of 50 mgm/kgm body-weight for aspartame?

Even though the FDA seemingly declined to apply the provisions of the Delaney Amendment in this case, they could have still elected to subject the data on brain tumors to a formal Risk Assessment or Risk Analysis; this is a procedure on which they have a regulation and FDA policy is to carry out such formal Risk Assessment in the case of suspected carcinogenic agents which find their way into human food through exposure to them by food-producing animals. In other words, this is not some kind of technique that would be new or unfamiliar to that regulatory agency. And yet, it appears that either that specific procedure was not attempted at all in the FDA as far as aspartame is concerned, or, if attempted, its results were set aside or ignored.

In this section I shall present the results of my own computations involving the risks of brain tumors; the specific set of data analyzed has been given in the previous section here -- the incidences of such tumors as tabulated by Dr. Olney in his presentation before the Scientific Board of Inquiry with respect to aspartame.

The first item to be considered is that if one wishes to extend safety data from small laboratory rodents such as rats to much larger mammals such as humans, the exposure rates expressed in grams per body-weight must be modified or corrected by a certain adjustment.

The reason for this is that relatively small animals have, per unit body-weight or mass, a much larger body-surface. It is well known that most metabolic functions are better related to body-surface than they are to body-weight. For example, if one were to provide general anesthesia, say, for an elephant, and one were to select the same dose in mgm/kgm body-weight of a general anesthetic which is used in humans, chances are excellent that the animal will promptly die due to a drug-overdose; the reason for this is the same -- for a given unit of body-weight, the elephant has a much smaller total surface area than the human and, therefore, a much lower tolerance for any drug given on a basis of body-weight.

The usual adjustment aimed at correcting this problem is to find what dose in humans is equivalent to a certain dose given to rats (expressed in grams per kgm body-weight). In the particular study of Searle where the brain tumors were found, the average adult weight of male rats was 506 gms. and that for female rats was 331 gms, for an average weight for the two sexes of 418.5 gms. A 60 kgm adult human is "worth" on a weight or mass basis 60,000/418.5=143.37 such rats. On a body-surface basis, however, that same 60 kgm. human would be "worth" only the two-thirds power of 143.37 i.e., only 27.39 rats of an identical average

weight. Thus, in order to have equivalence between humans and rats, doses expressed in grams/kgm body-weight for the rate must be divided by the one-third power of 143.37 i.e., by 5.23. It is clear that 5.23 X 27.39 is 143.37, the ratio of the body-weights for the two species.

The formal risk assessment was carried out by utilizing two separate techniques: one was the Mantel-Bryan approach (also known as the log-probitmethod) while the other was the so-called One-Hit procedure. The latter is defined as P(d) = 1 - exp(-lambdad) where P stands for probability, d for dosage, exp(iota) indicates e, the well-known mathematical constant, 2.718, raised to the power of -lambda, and lambda stands for a constant to be estimated from the observed experimental results.

The Mantel-Bryan procedure, published nearly a quarter century ago in 1961 in the Journal of the National Cancer Institute (Vol. 27, page 455, under the title "Safety Testing of Carcinogenic Agents") represents the first rational and formal approach at risk analysis; in the time elapsed since its publication it has gained extremely widespread recognition and acceptance. Such regulatory agencies as the FDA and the EPA use it routinely in their risk assessment procedures inasmuch as it is being generally regarded as a "classic" method.

I have used here both of these extrapolating techniques with a confidence interval of 90 percent, and in either case the Abbott Correction was utilized.

The table that follows presents the "virtually" safe levels of aspartame expressed in mgm/kgm body-weight corresponding to a variety of upper limits on the risk with the data derived, as explained, from the observations on brain tumors in rats as tabulated by Dr. Olney. The results for each of the two methods of extrapolation (the log-probit and the one-hit procedures) are presented for either rats or humans; as explained on the previous page here, the estimates for the human are 5.23 times smaller than those for the rat due to the necessary correction for the relative body-surface of the two species.

RESULTS OF THE FORMAL RISK ASSESSMENT

[Based on data for brain tumors in rats]

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Please refer to the table in the online document.

Extrapolating procedure: Upper limit on brain tumor risk	"Virtually safe" levels of aspartame expressed in mgm/kgm body-weight	
	One-hit method	
	For rats	For humans
1/100,000,000	0.000,731	0.000,140
5/100,000,000	0.003,66	0.000,699

1/10,000,000	0.007,31	0.001,40
5/10,000,000	0.036,6	0.006,99
1/1,000,000	0.073,1	0.014,0
5/1,000,000	0.366	0.069,9
1/100,000	0.731	0.140
5/100,000	3.66	0.699
1/10,000	7.31	1.40
5/10,000	36.6	6.99
1/1,000	73.1	14.0
5/1,000	366	69.9
1/100	735	140

Examination of the entries in the table just above reveals that for very small upper limits on the risk, the one-hit procedure yields estimates much smaller than those generated by the log-probit method: For an upper limit on the risk as small as 1/100,000,000, the one-hit estimates are some 520 times smaller than the corresponding ones resulting from the log-probit approach. However, for larger upper limits on the risk, this difference between the two kinds of estimates gradually disappears -- thus, for an upper limit on the risk as high as 1/100 the estimates generated by each of these two separate methods of extrapolation appear to be virtually identical.

If we now wish to enquire on the upper limit for the brain tumor risk associable with 50 mgms/kg body-weight for aspartame (the level that the FDA views as constituting an Allowable Daily Intake or ADI), we may consult the table on the previous page here; 50 mgms/kg body-weight for humans would fall between the entries in the third-last and the second-last row in that table; the upper limit on the risk would, therefore, be between 1 and 5 per thousand population for each of the two extrapolating procedures. More exact interpolation would yield for 50 mgm/kg body-weight for humans (equivalent to 261.69 mgm/kg body-weight for rats) an upper limit on the risk of 2.27/1,000 population under the log-probit kind of extrapolation and 3.57/1,000 population for the one-hit kind.

It is clear that risks of this magnitude for what the FDA regards as a "safe" level of exposure to aspartame represent an outright calamity or disaster. In fact, were the Allowable Daily Intake of aspartame be only ONE-TENTH as large as decreed by the FDA, i.e., in the neighborhood of merely 5 mgm/kgm body-weight, the table on the previous page reveals the upper limit on the brain tumor risk would still be as large as approximately 1/10,000 population for the log-probit method and almost 5/10,000 population for the one-hit procedure, both of which would seem to me to be clearly and totally unacceptable. Even if the FDA's ADI were one-hundred times smaller (i.e., no more than 0.5 mgm/kgm body-weight) the upper limit on the brain tumor risk can be seen in the table on the previous page here to be approximately between 1 and 5/1,000,000; considering the widespread consumption of soft-drinks containing this food additive in this country alone, I should think that even this would represent a rather high risk.

This concludes my remarks that were briefly summarized near the bottom of the

first page of this communication.

I should add here that the views given above are strictly my own and that they do not represent in any way those held by the U.S. Environmental Protection Agency where I am currently employed; that agency has no regulatory jurisdiction or interest in food-additives such as aspartame.

Wishing you and Senator Metzenbaum the very best and continued success in all your legislative efforts, and particularly those that involve aspartame, I remain, Mr. Wagoner,

Sincerely yours,
M. Adrian Gross,
SENIOR SCIENCE ADVISOR,
BENEFITS AND USE DIVISION,
Office of Pesticide Programs.

STATEMENTS FROM COMMUNITY NUTRITION INSTITUTE

A national organization, Aspartame Victims and Their Friends, Inc. was launched today at a Washington, D.C. press conference in which one of the organization's founding members announced that a lawsuit would be filed against G. D. Searle and Company, makers of aspartame under the trade name NutraSweet.

The organization, which is affiliated with the Aspartame Resource Center of the Community Nutrition Institute, a Washington-based consumer group, will be located in Ocala, Florida, and will operate a national telephone hot line.

A founding member of the organization, Mrs. Shannon Roth, Ocala, who recently lost vision permanently in one eye, said the onset of her blindness began with the use of NutraSweet and her vision deteriorated over a period of several months during which she consumed large amounts of the sweetener. Her loss of vision is linked to aspartame by her physician and other medical authorities.

Roth said she is filing a personal injury lawsuit against Searle in Florida, and that she is joining with several other members of "Victims" to file a personal injury claim against the Food and Drug Administration (FDA). James Turner, an attorney and consumer activist, said that an administrative petition is being filed with the Justice Department as the preliminary step toward the eventual personal injury lawsuit against FDA.

CNI's Executive Director, Rod Leonard, said the new organization would provide a link between aspartame users who have experienced adverse reactions and have suffered injury and economic loss. He described the symptoms which include grand mal seizures, severe suicidal depression, temporary and permanent blindness, menstrual problems and other severe disorders.

Leonard said that he and Turner also are filing a request with FDA to create a national surveillance program on aspartame complaints. He said FDA