Note: This letter is on EPA Stationary

Senator Howard M. Metzenbaum, (Dated 3 November, 1987) United States Senate, 140 Russell Senate Office Building, Washington, DC, 20510

Dear Senator Metzenbaum,

The following is in response to a request for comments addressed to me by Mr. James C. Wagoner of your Office in reference to the safety of the artificial sweetener aspartame, known commercially as Nutrasweet.

As you may know, during my service with the FDA from 1964 to 1979 I participated along with others in the extensive investigation of the quality of experimental studies carried out by or for the G.D. Searle & Co. of Skokie, Ill. Inasmuch as I had participated both in the "on-site" investigations as G.D. Searle & Co., as well as in the evaluation of the findings that emerged, my signature along with those of others appears on the final report of that FDA investigations (known also as the Searle Task Force Report) which was dated March the 24th, 1976.

In early 1979 I was transferred for duty from the FDA to the EPA to assume a position involving a promotion for me. My comments here ought not to be taken to imply in any way that they represent the views of the EPA since this agency has no regulatory concerns whatsoever in the area of food additives; rather, such comments of mine represent strictly my own views.

During that 1975 FDA investigation at G.D. Searle & Co. and at a number of their contractors, a total of 25 distinct experimental studies were intensively audited. Almost half of those 25 studies (11, to be exact) were carried out for aspartame with the remaining 14 studies having been distributed amongst 6 drug products manufactured by G.D. Searle & Co. It is worthy of note that the conduct of all experimental studies by that firm, regardless whether they entailed food additives or drug products, was the responsibility of a single group in the G.D. Searle & Co.'s organization:- the Pathology-Toxicology or Path-Tox Department. Practices that were noted in connection with any given such study were quite likely to have been noted also for other studies that were audited, and this was a situation which was in no way unexpected:- after all, the set of all such studies executed by that firm from about 1968 to the mid 1970's were conducted in essentially the same facilities, by virtually the same technicians, professional workers and supervisors, and the nature of such studies does not differ much whether a food additive or a drug product is being tested for safety in laboratory animals. It is in this sense, therefore, that the overall conclusions summarized at the beginning of the Searle Task Force Report have relevance to a all the studies audited in 1975 (whether they had reference to aspartame or to any of the six drug products of Searle's) and, by extension, to the totality of experimental studies carried out by that firm around that time - 1968 to 1975.

The FDA's Task Force Report starts at the top of its page 1 with:-

"At the heart of the FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our

investigation clearly demonstrates that, in the (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 un- der 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 of 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 ques- tions of an FDA reviewer. Finally, we have found instan- ces of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly execu- ted, or inaccurately analyzed or reported."

"While a single discrepancy, error, or inconsisten- cy 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 error blur the differences between treated and control animals and in- crease the difficulty of discriminating between the two populations to detect a product-induced effect. A posi- tive 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 those general comments and references to no basis for reliance on reports generated by the GD Searle Company, serious deficiencies in Searle's operations and practices, Searle's integrity, Searle's selectively reporting the results, poorly conceived, carelessly executed and inaccurately analyzed or reported experiments at Searle's, a pattern of conduct which compromises the scientific integrity of the studies, pervasive problems in the Searle studies, their unreliability, etc., which apply across the board to all studies investigated, there are a number of additional problems that attach specifically to the aspartame studies. These are discussed in the FDA's Searle Task Force Report in its

page 25 - paragraph 1 - on the identity of the material tested;
page 26 - last paragraph - on the excision of tumor masses ante-mortem and writing the protocol after the start of a study;
page 31 - paragraph 2 - on Searle tactics designed to obtain FDA approval for aspartame;
page 32 - last paragraph - on continuity of personnel at Searle and on the adequacy of their training and supervision of such personnel;
page 33 - paragraph 2 - on practices which could compromise the study; - paragraph 3 - on improper departure from protocol specifica tions on age of the animals used;
page 34 - paragraph 2 - on deviations from protocol at Hazleton Labo- ratories;
page 36 - paragraph 3 - on the lack of concern both at Searle and at Hazleton Laboratories over the homoqeniety, or stability of the ingredient-diet mixture; subsequent paragraphs deal with the same sort of problems at Hazleton Laboratories and it is concluded that "there is no way in which it can be assured that animals received the intended dosage.";
page 39 - paragraph 1 - on the improper use of pesticides in the areas where the studies were carried out; on the condition of the blenders used to mix the test agent in the diet; on the lack of records on mixing operations; on the conditions of the labels of the mixtures; on the lack of inventories of the test substance;
page 42 - paragraph 1 - on the records kept of the observations made and on the numerous errors and inconsistencies amongst observations and findings;
page 47 - near bottom - on the impact of the errors in the records of observations;
page 51 - paragraph 1 - on the excision of tumor masses; see also page 52, paragraph 1 there for the impropriety of this practice;
page 52 - last paragraph - on the "substantial" loss in pathology infor- mation due to autolysis, fixation "in toto", etc. page 55 - top - on the impropriety of changing a prosector's observations by others who did not participate in examining the carcasses of the animals;
page 57 - paragraph 2 - on the poor quality of material prepared for microscopic examination of the tissues;
page 60 - paragraph 3 - on observations being reported for material that never existed; this problem was noted at both Searle and Hazleton Laboratories;
page 62 - paragraph 2 - on the lack of training by the "professional" scientists making observations in teratogincity studies;
page 64 - paragraph 3 - on the abysmal quality of the aspartame tera- tology and reproduction studies and on an evaluation of these by a leading international British expert in this area;
page 66 - paragraph 3 - on the serious problems with the Waisman study of Aspartame in monkeys;
page 80 - top - on the false values presented by Searle on observations collected during the aspartame studies in hamsters, with reference to blood, clinical chemistry, etc., and the improper filtering of results from the 115 week rat study with aspartame.

It should be pointed out that the Task Force Report detailing those general conclusions as well as those that relate specifically to the aspartame studies are not merely the views of the members of the Task Force itself. That Task Force operated under the direction of a Steering Commit- tee composed of a number of FDA Bureau Directors as well as others and the Chairman of that Committee was none other then

the FDA Commissioner himself. In fact the Task Force Report was addressed to the Commissioner in his capacity as Chairman of the Steering Committee, and, it seems clear that both the Committee and the Commissioner accepted that report and transmitted it to the United States Senate as an institutional FDA report without changing in it as much as a semicolon. The following are quotes from pages 3 and 4 of the record of hearings of April 8-9 and July 10, 1976, held by Sen. Edward Kennedy, Chairman, Subcommittee on Administrative Practice and Procedure, Committee on the Judiciary, and Chairman, Subcom- mittee on Health, Committee on Labor and Public Health:-

page 3 of the record - Commissioner Schmidt of the FDA :- "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 - Senator Kennedy (addressing Commissioner Schmidt):- "Let me ask you this. These are the conclusions of the (Task Force appointed to that) study. Do you agree with those conclu- sions?"

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 examinations' 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 iso- lated problems, but we were not aware of the extent of the problem in one pharmaceutical house..."

Given those conclusions reached on the quality of Searle experimental studies in general and of the aspartame studies in particular, as we have seen above, by both the FDA as an institution and its Commissioner in 1976, how is it possible for another Commissioner in July, 1981, to reapprove the use of aspartame being marketed in dry foods? How is it possible for yet another Commissioner two years later, in July, 1983, to have extended such approval for marketing aspartame also in carbonated beverages? Such approvals were based on largely the very same studies that were examined by the Task Force in 1975-76.

It seems to me that no amount of additional examinations of pathology material such as undertaken by the UAREP and others, now additional statis- tical analyses carried out on the data, and no judgmental evaluations or interpretations of any data arising from those studies can in any way rectify the basic problem expressed by the Task Force, i.e., the FDA itself: in the absence of reasonable expectation that the experimental animals were administered the correct dosages of the test agent, any obser- vational data carried out on those animals must be regarded as questionable or flawed. This is to say nothing of all the myriad of other problems involving the competence of those conducting such studies, and the care they exercised in their execution. Once a study is carried out and the test animals are disposed of, all that remains are the number of tiny bits of fissure preserved from their organs for

microscopic examination and the written records of observations made by those who actually carried out that study. While the tissues themselves can be examined by others long after the remains of those animals no longer exist, the reliability of the written records has already been found to be unacceptable in a great variety of ways. Clearly, there is no way that even the most competent scientists can make any new observations on those animals at a time subse- quent to the conduct of the study. Once a study is compromised in its executions, it is beyond salvation by anyone.

Even with respect to those small portions of tissue preserved for microscopic examination for an indefinite period of time after any study is completed there are serious problems as presented in the 1976 FDA report with respect to Searle studies in general and for the aspartame studies in particular:- there is little if any assurance that such samples of tissues as were preserved actually originate from the specific animals said by Searle or Hazleton to have been their source (see the discussion on page 57 paragraph 2 et seq.) Furthermore, due to the unacceptably high rate of post-mortem autolysis, a great many such tissues were not collected at all from the experimental animals. In any such study of even a few hundred test animals, it takes no more than a dozen or so of them to exhibit a particular lesion (such as brain tumors, for instance) where missing no more than one or two animals manifesting such tumors in any given exposure group may well make the difference whether that particular lesion is or is not significantly associated with the test agent, i.e., aspartame or any of its related chemicals.

Following the Senate hearing in the Spring and Summer of 1976, during the winter beginning in that year the FDA began negotiating with GD Searle & Co. on retaining the UAREP (Universities Associated with Research and Education in Pathology), a private organization, on the feasibility of investigating a number of other Searle studies with aspartame. Whin I heard of those negotiating being in effect, I wrote a memorandum to Mr. Carl Sharp, the chairman of the FDA's Searle Task Force, on November the 4th, 1976. a copy of it is given here as Attachment 1, and my apprehen- sions over such plans is clearly evident there. Basically, they amounted to the fact that the UAREP was totally unsuited for such task since it had never before engaged in anything like it and I also objected to the idea that Searle was to fund that particular activity by the UAREP. As men- tioned there, the FDA had just received a supplemental appropriation from the US Congress for the express purpose of expanding its own activities in that very area of investigating the conduct of such experimental studies by the regulated industry. Under that appropriation (which came to some $16,000.000) a great number of additional investigators were hired and trained for this particular task by the FDA.

A few months prior to the UAREP beginning its investigations in August of 1977, in April of that same year, yet another FDA investigation of three aspartame studies conducted at GD Searle & Co. was undertaken. The 76-page report of that investigation (also known as the Bressler report, after the name of the leader of the investigative team, Mr. Jerome Bressler, a compliance officer in the FDA's Chicago District) reveals the reference to a single one of those studies (the 115-week experiment in rats exposed to DKP or diketopiperazine, a breakdown product of aspartame) the following:-

- substitutions of some of the animals in that study; - the presence of intercurrent disease amongst the test animals and the administration of drugs to combat this, neither of which were completely reported to the FDA; - incomplete examinations of tissues from the experimental animals; - excision of tissue masses likely to be tumors from live animals during the study; - absence of batch records for the mixing of the test substance into the diet of the test animals; - incomplete stability studies for the agent on test; - absence of homoqeneity 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 the DKP that was given to those rats; - problems with the fixation-in-toto and autolysis; - failure to report to the FDA all tissue masses (likely to be tumors) which were found in the experimental rats; - failure to report to the FDA all internal tumors present in the experimental rats, e.g., polyps in the uterus (animal K9MF), ovary neoplasms (Animals H19CF, H19CF, and H7HF) as well as other lesions (Animal D29CF); - inconsistencies between different parts of the report on this study submitted by GD Searle & Co. to the FDA on the precise nature of the lesions manifested by the test rats; - numerous transcription errors in that report.

Interestingly and most important, the Bressler investigating group found not only that no homogeneity test were conducted by GD Searle & Co. on the mixture of the test agent within the animals' diet, but they actually obtained direct evidence that in fact the distribution 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. Descriptive remarks on this issue were found by the FDA investigators in a notebook kept by Searle personnel on observations made during the study, as was a Polaroid photo-graph taken by the same Searle technicians and which clearly shows the test agent in the form of coarse particles with the animals' diet. If follows that the experimental rats could have consumed their feed without actually touching the DKP and, consequently, no-one can state with any assurance whatsoever just how much DKP (if any) those rats were actually exposed to in the course of that study. Evidence such as this obtained by the FDA investigators seems to me to have been crucial to the interpretation of any findings or observations by Searle.

On page 32 of the GAO report one can read the view of the FDA's Center for Food Safety and Applied Nutrition (CFSAN) on the findings of the investigators. To me these read like a script written for Abbott and Costello in the sense of their having their perceptions inside-out or upside-down - "the diets may have been homogeneous because of a dose-related increase in the incidence of uterine polyps and decrease in blood cholesterol levels" (a clear non-sequitur, such as one almost never encounters in real life); on the problem with autolysis of the tissues the CFSAN felt "they could not determine whether the results would have been altered if these tissues had been obtained before autolysis (an obvious instance of placing the burden of proof that a study is unsound on the Government rather then requiring the petitioner for approval of a food additive to demonstrate, as the Law requires, that any study is of sound quality); the observation by the investigators that 329 fetuses were examined in two days by a single person (a clear impossibility) was laid aside by the CFSAN with another non-sequitur:- that "the Searle scientist who performed these examinations estimated that he examined about 30 fetuses a day..."; on the fact that an insufficient number of sections were made out of the heart, the CFSAN observed:- "...while there was no evidence that the study was compromised by this issue, the practice of not

making enough sections through the organs, as specified in the protocol, did not preclude a possible failure to observe abnormalities which may have occurred."

Despite all these problems, at least some of which undermined or compromised the study in an unredeeming manner, apparently the CFSAN and the FDA Commissioner found the quality of those three studies reported on by the Bressler investigating group as being in fact of an acceptable nature and GD Searle & Co. were notified to this effect in September, 1977.

The investigation undertaken by the UAREP began in August, 1977. After reading the report of that group, it became painfully clear to me that the misgivings which I foresaw in November 1976 (see Attachment 1 here) were indeed justified and my worst fears were eventually realized. If one compares the kind of detailed and painstaking findings made by the professional investigators from the FDA both in 1975 and in 1977 with the rather amateurish activities by the UAREP outlined in their report, the contrast between these could hardly have been greater. Of course, inasmuch as GD Searle had paid for the UAREP investigation, the cost of it for the FDA was nil; what the FDA got in return for its money, was not worth much more than this.

Perhaps the most disappointing aspect of this entire fiasco with the quality or reliability of the experimental studies with aspartame was the failure of the Public Board of Inquiry (PBOI) to consider these aspects in their deliberations. The PBOI expressly declined to do so even after the principal objectors to the approval of aspartame for marketing, Mr. James Turner and Dr. John Olney, asked for such consideration. To me it seems almost beyond belief that a collection of scientists can sit on judgement over the interpretations to be made on a set of results arising from certain studies, not only failing to consider the adequacy of the conduct of those studies but actually refusing to do so.

Given this sort of circumstance, it should not come as a surprise to anyone that eventually the Commissioner of the FDA finally reapproved aspartame for marketing even though his own panel of experts were divided over the issue whether this particular food additive had been shown in a reasonable manner to be safe.

As mentioned in the GAO report (page 12 there) "The Federal Food, Drug, and Cosmetic Act does not specifically define 'safety'. However, the legislative history of the Food Additives Amendment indicates that safety means "proof of a reasonable certainty that no harm will result from the proposed use of an additive'." It is intuitively clear to anyone that no "reasonable certainty" can attach to any results emanating from studies as profoundly flawed as the Commissioner of the FDA had determined in 1976 and as amply reconfirmed since then.

This concludes my remarks on the quality or reliability of the experimental studies with aspartame carried out by the GD Searle & Co. or by the contractors working under the direction of that firm.

Since Mr. Wagoner of your Office has requested my comments in a very short period of time, I am expediting this letter to you now; however, I plan to send you in the very near future an additional communications where two other issues are

discussed in some detail:- the problem with the brain tumors induced by aspartame and that the FDA's having set a very high (and, to my view, clearly dangerous) level of Acceptable Daily Intake, or ADI, for this particular food additive in the diet of humans.

Finally, I wish to state here that, quite aside from my professional background as a scientist and speaking merely as an individual citizen, I am grateful for the concern you have had over the safety of aspartame for many years now; as such, I wish to thank you for having given me this opportunity of being of some service to you. With best wishes for the future, I remain, Senator Metzenbaum,

Sincerely yours,

M. Adrian Gross, Senior Science Advisor, Benefits and Use Division, Office of Pesticide Programs Sworn to be a true copy on 30 Oct, 1987.

Note: This letter is on EPA Stationary

Senator Howard M. Metzenbaum, (Dated 3 November, 1987) United States Senate, 140 Russell Senate Office Building, Washington, DC, 20510

Dear Senator Metzenbaum,

The following represents a continuation of my letter to you of last week, October the 30th, 1987. In that letter I discussed the many serious problems with the quality or reliability of the experimental studies with aspartame carried out by or for G.D. Searle & Co.; I noted there that in 1976, the FDA Commissioner at that time, Dr. Alexander Schmidt, speaking for the FDA as an agency, publicly stated that he agreed with a set of conclusions, the first of which was that the FDA had no basis for reliance on the quality of studies generated by or for that firm.

Once such a determination is made at the highest level of the FDA, it seems bizarre, to say the least, that essentially the same set of studies could provide a foundation for the subsequent decision that those studies in fact had demonstrated the safety of aspartame with "reasonable certainty" as required by the Food Additive Amendment of the Federal Food, Drugs, and Cosmetics Act. As the television commercials for Weyerheauser, the "tree-growing company", keep telling us:- "once the eagles are gone, they are gone."

Much the same is true also for experimental or laboratory rats:- once they are gone, no one can bring them back for an interview to ask them how much, if any, aspartame or DKP they had ingested while the experimental studies in which they had participated were in progress and, without such essential information, examination of their preserved tissues by even the most skillful and competent of pathologists becomes largely a meaningless exercise which cannot in any way resurrect in Phoenix-like fashion the value of those studies.

However, having said all of this, let us assume that in fact those studies were of an acceptable quality; let us pretend that the test animals were actually exposed qualitatively and quantitatively to what G. D. Searle & Co. would have us believe that they were exposed; that there was no post-mortem autolysis of their carcasses rendering vast numbers of their tissues to a state unsuitable for pathology examination; that the technicians involved in the conduct of those studies were fully trained, competent, and adequately supervised to make observations on those animals prior to their death; that the same was true with respect to the observations made after their death; that in fact those technicians actu- ally made proper such observations; that the proper samples of tissues with grossly observed lesions were in fact collected for additional microscopic examination; that the identity of such tissue specimens corresponded (as they should) to the identity of each animal that was their source, etc. In short, let us make believe in a spirit of Halloween that nothing which was uncovered for the aspartame studies by the FDA investigations of 1975 and 1977 was actually true, i.e., that in fact we are dealing here with studies of an absolutely perfect quality or reliability. Of course, such assump- tions belong to the domain of Fantasyland, but, nevertheless, let us play this little game for awhile.

Under such highly speculative hypothetical conditions, let us now ask again whether aspartame can be viewed as being safe with "reasonable cer- tainty".

To answer this question, let us focus for a moment on the pathology examinations carried out not by the pathologist originally retained by GD Searle & Co. (those of the Experimental Pathology Laboratories, or EPL) who examined the tissues from the rats in the Two-Year Rat Study) but, rather, on the examinations carried out by the expert pathologists in the UAREP. Although in my last letter addressed to you last week I referred to the investigative efforts of the UAREP as being "amateurish" by comparison with those of the professional investigators in the FDA, I have no reason to question or criticize in any way the competence of UAREP pathologists in their own specialty where they had examined first-hand tissue specimens said to gave been collected from the animals in that study.

The UAREP report (Volume 2, Chapter IV, dealing with that particular study, reveals in Appendix IV-21 on its page 393 et seq. the animals which were found by the UAREP pathologist to have harbored brain tumors:-

Group Sex Path.No Animal No. Type of brain tumor Weeks to death 1 M 64-603 83-651 Astrocytoma 104 2 M 64-775 83-745 Astrocytoma 104 3 M 64-764 83-837 Astrocytoma 76 4 M 64-707 83-919 Astrocytoma 104 M 64-712 83-888 Oligodendroglioma 59 M 64-713 83-892 Astrocytoma 49 M 64-715 83-895 Astrocytoma 100 5 M none 1 F none 2 F 64-989 83-769 Astrocytoma 104 65-011 83-766 Astrocytoma 69 3 F 4 F 64-925 83-934 Astrocytoma 85 5 F 64-881 84-010 Medulloblastoma/ meningeal sarcoma 13 64-888 84-019 Astrocytoma 67

Altogether the table just above lists a total of 12 animals with brain tumors, 7 males and 5 females; for both sexes there are 1 in Group 1, 3, in Group 2, 1 in Group 3, 5 in Group 4, and 2 in Group 5 for a total of 12. Note that the GAO report which refers to those animals at the bottom of its page 45 is in error in that it lists 4 (rather than 3)

animals with brain tumors in Group 2 (the low dosage group). Because of this error, the GAO's Figure 4.1 on page 46 of its report is somewhat misleading.

The GAO report also indicates under item (2) on its page 34:- "According to UAREP's president at the time of its review" "...the thing that impressed (UAREP) throughout the study,... which is reflected in our final statements and conclusions, was that the interpretations of the experimental results by previous observers did not really differ very significantly from ours following our review of the material."

Yet, Appendix IV-25 beginning on page 446 of the UAREP report repre- sents a 6-page table entitled "Significant Discrepancies Between Histo- pathologic Diagnoses By UAREP and EPL", the last mentioned having been, as stated above, the "previous observers", i.e., the pathologists originally retained by GD Searle & Co. to examine those tissues and whose report was submitted by that firm to the FDA in support of their petition to have aspartame approved for marketing. In that table I have counted some 207 such "significant discrepancies" between the diagnoses of the UAREP and EPL and these involve some 162 animals or 37% of all the 440 animals in that study. This was not reported by the GAO representatives who apparently were content with merely chatting with the UAREP president about his reminiscences of some 10 years ago.

Moreover, that same UAREP report reveals in that very same Appendix IV-25 as cited above for the 12 animals with brain tumors the characteri- zations or diagnoses reached by the pathologists from the EPL:-

for animal No. 83-651 with an astrocytoma of the brain EPL lists the brain as unremarkable; for animal No. 83-745 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-837 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-919 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-888 with an Oligodendroglioma of the brain EPL lists no comparable diagnosis; for animal No. 83-892 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-895 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-769 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-766 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-934 with an astrocytoma of the brain EPL lists an ependymomo\a i.e., a different kind of brain tumor; for animal No. 84-010 with a medulloblastoma/meningeal sarcoma of the brain, EPL lists a meningioma i.e., a tumor of the membranes covering the brain; for animal No. 84-019 with an astrocytoma of the brain there was no discrepancy in the EPL diagnosis.

In other words, for the 12 animals identified as having brain tumors in this study by the UAREP pathologists, EPL pathologists (i.e., the "pre- vious observers" as the president of the UAREP has it) had completely missed no less than 9 or 75% of these. Such difference between the diagnoses of those two groups cannot by any stretch of the imagination be interpreted by any reasonable person as being "not very significant" as that same president of the UAREP is quoted by the GAO to have stated. Incidentally, the GAO representatives themselves also failed in their report to highlight this tremendous difference between the diagnoses of the UAREP and EPL.

Furthermore, Appendix IV-20 on page 391 of that same UAREP report reveals in the first row of the table on that specific page that GD Searle & Co. or their agents had provided to the subcontracting EPL pathologists, i.e., to those whose report that firm had originally submitted to the FDA:-

a) only 8 (or only 10%) of the brain sections for the 80 animals in group 2;

b) only 7 (or only less then 9%) of the brain sections for the 80 animals in Group 3;

c) only 5 (or only less than 7%) of the brain sections for the 80 animals in Group 4;

and the UAREP were proved with the brain sections of 2 fewer animals than were provided to the EPL. Again, this is another little wrinkle not high- lighted in the GAO report.

This, quite by itself, is sufficiently eloquent on just how G.D. Searle & Co. saw fit to discharge their responsibilities in reporting fully and completely their results of the Two Year Rat Study with aspartame to the FDA; it is just as eloquent on precisely how thoroughly the Bureau of Foods of the FDA (the predecessor of the CFSAN) had reviewed the data emanating from that study prior to its initial approval in 1974 for the marketing of that food additive.

I note at the bottom of page 54 in the GAO report that CFSAN had objected to the medulloblastoma that was noted in a female rat at the top exposure level on the grounds that "it was unlikely aspartame caused this tumor". Such statement would imply that aspartame had caused all the other tumors (the nine astrocytomas and the solitary oligodendroglioma noted in animals exposed to it) which is vastly more than enough to lead to a conclusion that, because of this, it cannot be regarded as being a safe food additive. The reason for such conclusion by the CFSAN appear in the first paragraph of page 46 of the GAO report. As is also true for many of the other arguments advanced by the CFSAN and by G.D. Searle & Co., those reasons are largely speculative and without much merit. Still, to accom- modate the CFSAN's views regardless of their validity, I am willing to ignore the occurrence of that particular tumor in a female animal at the top exposure level.

If we are to analyze the distribution of the rest of those brain tumors, we ought ignore also the response of any animals at the top level of exposure (Group 5) on the grounds that completing toxicity may well have inhibited the expression of brain tumors in the animals of that group.

Accordingly we have for the male animals with brain tumors:-

in Group 1 i.e., at 0 mcm/kgm body-weight 1/59 = 1.69% positive rats;

in Group 2 i.e., at 1,000 mcm/kgm body-weight 1/36 = 2.78% positive rats;

in Group 3 i.e., at 2,000 mcm/kgm body-weight 1/40 = 2.50% positive rats;

in Group 4 i.e., at 4,000 mcm/kgm body-weight 4/40 = 10.00% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,019,865 with standard error of only 0.000,009,729,2 leading to a chi square with one degree of freedom for slope as high as 4.118, whose one-sided probability is as low as p = 0.021,217; in other words, the

dose-dependent increase in frequency of brain tumors for the male rats in that study was highly significant and, therefore, attributable to aspartame, the agent on test.

That particular slope of the dose-response function yields the follo- wing expected incidences of brain tumors amongst male animals:-

at 0 mcm/kgm body-weight - 0.867% at 1,000 mcm/kgm body-weight - 2.854% at 2,000 mcm/kgm body-weight - 4.840% at 4,000 mcm/kgm body-weight - 8.813%

Note that the four expected values given just above are fairly close to their respective observed values listed near the bottom of the preceding page, which indicates a close fit of the observations to the dose-response or regression function.

If we have reference to the animals of both sexes with brain tumors, we have:-

in Group 1 i.e., at 0 mcm/kgm body-weight 1/118 = 0.847% positive rats; in Group 2 i.e., at 1,000 mcm/kgm body-weight 3/ 76 = 3.948% positive rats; in Group 3 i.e., at 2,000 mcm/kgm body-weight 1/ 80 = 1.250% positive rats; in Group 4 i.e., at 4,000 mcm/kgm body-weight 5/ 80 = 6.250% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,011,578 with a standard error of only 0.000,005,831,8 leading to a chi square with one degree of freedom for slope almost as high as the one for merely the male animals, 3.920, with on-sided probability almost as low as that for merely the male animals, p = 0.023,860. The conclusion that follows is identical with that reached above for merely the male animals.

The expected incidences for both sexes are:-

at 0 mcm/kgm body-weight - 1.006% at 1,000 mcm/kgm body-weight - 2.164% at 2,000 mcm/kgm body-weight - 3.322% at 4,000 mcm/kgm body-weight - 5.638%

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Note that in the analyses outlined above I have not combined the response noted at two or more experimental groups, as was done by the PBOI and as objected to by the CFSAN.

If we now analyze the data in the same "uncombined" fashion, while still excluding from consideration the medulloblastoma manifested by a female in the top exposure level group, and even if we do consider the poor response of the animals in the top exposure level group (which, as noted, may have been due to competing toxicity interfering with the expression of brain tumors), but consider the so-called "historical control" incidence of brain tumors (49/59,812 cited by Dr. Olney in his table 2 on

page 2 of Part III of his written statement presented to the PBOI as well as the rate of 4/115 positive control animals noted by both the UAREP and EPL for the Lifetime Toxicity study of aspartame in the rat - see UAREP report, Chapter V, page 559) along with the contemporaneous (local) control rate of 1.118 positive animals of both sexes noted in the Two-Year aspartame study in the rat, we end up with a total of 54/60,045 = 0.090% for the control inci- dence for both sexes. The weighted averages of the exposure level in Group 5 animals was 7,420 mgm/kgm body-wieght. Accordingly we would have:-

at 0 mcm/kgm body-weight - 54/60,045 = 0.090% rats with brain tumors; at 1,000 mcm/kgm body-weight - 3/ 76 = 3.947% rats with brain tumors; at 2,000 mcm/kgm body-weight - 1/ 80 = 1.250% rats with brain tumors; at 4,000 mcm/kgm body-weight - 5/ 80 = 6.250% rats with brain tumors; at 7,420 mcm/kgm body-weight - 1/ 77 = 1.299% rats with brain tumors;

This distribution yields a slope of dose-response function as high as 0.000,005,297 with a standard error of only 0.000,000,423,4, leading to a chi square with one degree of freedom for slope as high as 156 whose one- sided probability is as low as 4.031E-36, i.e., 4 with 35 zeros ahead of it and to the right of the decimal point. This is nothing short of astronomi- cally high significance.

Alternatively, if one considers merely the contemporaneous or local control value in the two-year rat study with aspartame, 1/118 = 0.85% ani- mals positive for brain tumors, the response at the lowest level of expo- sure, 1000 mgm/kgm body-weight, 3/76 = 3.95% animals similarly positive for brain tumors, is elevated by comparison with that control rate more than 4.5 times which is borderline significance at p = 0.058,674. The response at the next to the highest level of exposure of 4,000 mgm/kgm body-weight, 5/80 = 6.25% animals with brain tumors, is elevated more than 7.3 times over that same control rate of 0.85%, and this is highly signifi- cant at the p = 0.009,975 probability level.

Finally in this entire consideration of significance for the brain tumors, one could set up yet another sort of contrast by making believe that all animals exposed to aspartame were in fact exposed to the highest level tried, 7,420 mgm/kgm body-weight. This would extend a great deal of the benefit of doubt to aspartame. that particular contrast of 0.090% the control rate versus 10/313 = 3.195% for all exposed animals (still excluding the medulloblastoma objected to by the CFSAN), leads to a chi square adjusted for continuity and with one degree of freedom as high as 254 which is, again, of almost astronomical significance.

In other words, even if one is willing to give aspartame a very generous benefit of doubt on the quality or reliability of the two-year study in rats as well as several other considerable benefits of the doubt involved in the test of significance, it still emerges that the rate of brain tumors amongst the animals exposed to it vastly exceeds that for animals not exposed to it and such excess is very highly significant. What this says is that there cannot be any reasonable, or even shadow of a doubt that aspartame had caused such an increase in the incidence of brain tumors.

It follows, therefore, that the conclusion of the PBOI and of several members of the FDA Commissioner's panel of experts is the right conclusion, and that reached by the

CFSAN and by the FDA Commissioner who overturned the PBOI view in this respect is the wrong conclusion.

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The Acceptable daily Intake (ADI) of aspartame.

Still under the hypothetical assumption that these experimental stu- dies were of an impeccable quality, let us now turn to a different aspect of the interpretation of results arising from them.

Near the bottom of page 60 of the GAO report it is disclosed that the Acceptable Daily Intake (ADI) of aspartame was raised from 20 mgm/kgm body- weight to 50 mgm/kgm body-weight after aspartame was approved for use in carbonated beverages and after it became evident to the FDA that very young children could potentially consume almost 50 mgm/kgm body-weight of it per day.

It appears that the justification for such sudden and considerable in- crease of 150% in the ADI for aspartame was provided by the results of five clinical studies as well as five other studies published in the literature; however, it is unclear from the GAO report whether any of those studies were of a long duration (such as a major part of the life-span) - clearly, such studies conducted with humans could not possibly have been of this nature.

To examine whether an ADI of 50 mgm/kgm body-weight can be justifiably regarded as "safe", let us return to the issue of the brain tumors and conduct for these a formal Risk Assessment. Although it has been esta- blished here that the incidence of brain tumors in rats was highly signifi- cantly related to the dosage of aspartame in the two-year rat study (and, therefore, that aspartame had cause that increase in incidence of brain tumors amongst exposed animals by reference to the rate noted in comparable unexposed ones) such determination of high significance is in fact not a necessary requirement for a formal risk assessment.

I have carried out such risk assessment by utilizing two separate pro- cedures which are widely accepted for this purpose:- the Mantel-Bryan ap- proach (also known as the log-probit method) and the Hone Hit method of extrapolation.

To extend again the benefit of doubt to aspartame, I have had refe- rence in such assessment to the control rate of brain tumors noted merely in the local or contemporaneous control animals (1/118 = 0.847%) rather then to the almost ten

times lower rate of the "expanded" control group discussed in the previous section here (54/60.045 = 0.090%); also, I have assumed all non-control rats to have been exposed at the top levels of exposure (7,420 mgm/kgm body-weight) rather then to a series of levels starting at merely 1,000 mgm/kgm body-weight; I have also excluded from consideration the medulloblastoma observed for Animal No. 84-010, but have not excluded the response of any other animal in that study. Each of these features, as mentioned, provides the benefit of doubt to aspartame, i.e., to its "producers" as distinct from its "consumers".

With such additional assumptions, we may tabulate the estimated "virtually safe" levels of aspartame in the mgm/kgm body-weight/day for a variety of upper limits on the risk indicated in the column at the extreme left of the table that follows here .

Note that for each of the two methods of extrapolation, two estimates are given in the table opposite each upper limit on the risk:- on for rats and one for humans. The estimate for the humans is related to the corresponding one for rats by being 5.23 time smaller then it. This is the factor necessary for "translation" from rats to humans by correcting for the body-area of the two species:- due to its larger size, the human has a body-area per unit mass smaller than does the rat:-

An average male rat in the study considered here weighed 506 Gms., and an average female rat 331 Gms., for a mean weight of 418.5 for the two sexes. This a human of average weight of 60 Kgms., say, is "worth" on a mass or weight basis 60,000/418.5 = 143.37 rats of average weight. But that same human weighing 60 Kgms is worth on a body-area basis only the two-thirds power of 143.37 i.e., only 27 .39 such rats. Thus, to have equivalence for doses expressed in mgm/kgms body-weight rats and humans, the dosage for the rats must be divided by the one-third power of 143.37, i.e., by 5.23. Hence the factor used in the table that follows.

RESULTS EMANATING FROM THE FORMAL RISK ASSESSMENT INVOLVING BRAIN TUMORS

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It turns out from the entries in the table just above that an ADI of 50 mgm/kgm body-weight for humans is associated by both methods of extrapo- lation with an upper limit on the risk as high as between 1/1,000 and 5/1,000 population exposed to aspartame to develop brain tumors as a result of exposure to that food additive. For this to actually become evident, it would take many years since such tumors have a very long latent period, i.e., it takes a long time for them to become manifest. Thus, it seems to me that we are dealing here with a huge time bomb.

There is hardly any need for me to emphasize here that this represents an unacceptably high risk or hazard posed by aspartame.

SUMMARY AND CONCLUSIONS.

From what has been discussed in my letter addressed to you last week as well as from what has been presented in the previous pages of this com- munication, I can conclude the following:-

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2. Even if, contrary to the FDA's view in 1976, the quality of the conduct of those studies could be relied upon by the same agency to even begin making such a determination, at least one of those studies had reveled a highly significantly dose-related increase in the incidence of brain tumors as a result of exposure to aspartame.

The full incidence of those brain tumors was not disclosed by G.D. Searle & Co. to the FDA prior to the initial approval for the marketing of aspartame in 1974; moreover, the review of that study in the FDA was so flawed that the Agency apparently did not even realize tat that time that only a portion of the observations on brain tumors had in fact been submit- ted by G.D. Searle & Co. in their petition for that approval.

3. Quite aside from the remarkable significance of the increased incidence with dose of those brain tumors, the ADI of 50 mgm/kgm body- weight recently set by the FDA for the human consumption of aspartame is alarmingly dangerous in that it involves an extremely high and, therefore, a totally unacceptable upper limit on the risk for those consuming aspar- tame: between 1/1,000 and 5/1,000 population to develop brain tumors as a result of such exposure.

4. Although in their report the GAO express the view that the FDA "followed its required process in approving aspartame (for marketing)" I would sharply disagree with such evaluation. Although the FDA may have gone through the motions or it may have given the appearance of such a process being in place here, the people of this country expect and require a great deal more from that agency charged with protecting their public health:- in addition to mere facade or window-dressing on the part of the FDA, they require a thorough and scientifically based evaluation by the Agency on the safety of the products it regulates.

Unfortunately this has clearly not been the case here. And without this kind of assurance, any such "process: or dance represents no more than a farce and a mockery of what is truly required.

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