UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Senator Howard M. Metzenbaum,
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 a 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 actually 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 assumptions belong to the domain of Fantasyland, but, nevertheless, let us play this little game for a while.

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

To answer this question, let us focus for a moment on the pathology examinations carried out not by the pathologists 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 have 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 pathologists 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
		64-712	83-888	Oligodendroglioma	59
		64-713	83-892	Astrocytoma	49
		64-715	83-895	Astrocytoma	100
5	M	none			

(continued on next page)

(Table continued from previous page)

Group	Sex	Path. No.	Animal No.	Type of brain tumor	Weeks to death
1	F	none			
2	F	64-989	83-769	Astrocytoma	104
		65-011	83-766	Astrocytoma	69
3	F	none			
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 interpretation 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 represents a 6-page table entitled "Significant Discrepancies Between Histopathologic 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 characterizations 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 ependymoma 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 "previous 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 the 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 than 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 provided with the brain sections of 2 fewer animals than were provided to the EPL. Again, this is another little wrinkle not highlighted 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 the 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 reasons 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 accommodate the CFSAN's views regardless of their validity, I am willing to ignore the occurence 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 competing toxicity may well have inhibited the expression of brain tumors in the animals in that group.

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

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

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

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

in Group 4 i.e., at 4,000 mgm/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 the 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 following expected incidences of brain tumors amongst male animals:-

at 0 mgm/kgm body-weight - 0.867%

" 1,000 " - 2.854%

" 2,000 " - 4.840%

" 4,000 " - 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 mgm/kgm body-weight 1/118 = 0.847% positive rats;

in Group 2 i.e., at 1,000 mgm/kgm body-weight 3/ 76 = 3.948% positive rats;

in Group 3 i.e., at 2,000 mgm/kgm body-weight 1/ 80 = 1.250% positive rats;

in Group 4 i.e., at 4,000 mgm/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 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 one-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 mgm/kgm body weight - 1.006%

" 1,000 " - 2.164%

" 2,000 " - 3.322%

" 4,000 " - 5.638%

or, again, fairly close agreement to the observed values given just above.

Note that in the analyses outlined above I have not combined the response noted at two or more experimental group, 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 the 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 incidence for both sexes. The weighted average of the exposure level in Group 5 animals was 7,420 mgm/kgm body-weight. Accordingly we would have:-

at 0 mgm/kgm body-weight 54/60,045 = 0.090% rats with brain tumors;

at 1,000 mgm/kgm body-weight 3/ 76 = 3.947% rats with brain tumors;

at 2,000 mgm/kgm body-weight 1/ 80 = 1.250% rats with brain tumors;

at 4,000 mgm/kgm body-weight 5/ 80 = 6.250% rats with brain tumors;

at 7,420 mgm/kgm body-weight 1/ 77 = 1.299% rats with brain tumors.

This distribution yields a slope of the dose-response function as high as 0.000,005,297 with 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 astronomically 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% animals positive for brain tumors, the response at the lowest level of exposure, 1,000 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 of 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% animnals with brain tumors, is elevated more than 7.3 times over that same control rate of 0.85%, and this is highly significant 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, rather than to various levels beginning at 1,000 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 if one is willing to give to 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 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.

As a result of all the considerations above, I would add my full endorsement to the conclusion of the unidentified statistician mentioned in paragraph 3 on page 56 of the GAO report who apparently reached the same conclusion as I did in an independent manner.

I would also support the views of the similarly unidentified carcinogenicity specialist mentioned in paragraph 2 of that same page in the GAO report who felt that the relatively high exposure rates in the two-year rat study with aspartame were a necessary compensation for the relatively low power of this study to detect as significant increases as high as 5% in the brain tumor rate for humans exposed to aspartame, which would constitute a downright catastrophe.

The Acceptable Daily Intake (ADI) of aspartame.

Still under the hypothetical assumption that these experimental studies were of an impecable 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 increase 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 long-term 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 established here that the incidence of brain tumors in rats was highly significantly related to the dosage of aspartame in the two-year rat study (and, therefore, that aspartame had caused 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 procedures which are widely accepted for this purpose:- the Mantel-Bryan approach (also known as the log-probit method) and the One Hit method of extrapolation.

To extend again the benefit of doubt to aspartame, I have had reference in such assessment to the control rate of brain tumors noted merely in the local or contemporaneous control animals (1/118 = 0.847%) rather than 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 level of exposure (7,420 mgm/kgm body-weight) rather than 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 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 on the next page.

Note that for each of the two methods of extrapolation, two estimates are given in the table opposite each upper limit on the risk:- one for rats and one for humans. The estimate for the humans is related to the corresponding one for the rats by being 5.23 times smaller than 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 a 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. Thus 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 mgms/kgms body-weight between 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

"virtually safe" level of aspartame in mgm/kgm bw/day

	Log-probit method		One Hit method	
Upper limit on risk	for rats	for humans	for rats	for humans
1/100,000,000	0.700	0.134	0.001,278	0.000,244
5/100,000,000	1.349	0.258	0.006,392	0.001,22
1/ 10,000,000	1.809	0.346	0.012,78	0.002,44
5/ 10,000,000	3.674	0.702	0.063,92	0.012,2
1/ 1,000,000	5.050	0.966	0.127,8	0.024,4
5/ 1,000,000	10.95	2.09	0.639,2	0.122
1/ 100,000	15.55	2.97	1.278	0.244
5/ 100,000	36.81	7.04	6.392	1.22
1/ 10,000	54.63	10.45	12.78	2.44
5/ 10,000	146.5	28.01	63.93	12.2
1/ 1,000	232.3	44.42	127.9	24.5
5/ 1,000	759.1	145.2	640.8	123.

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 extrapolation 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 communication, I can conclude the following:-

1. It is impossible for anyone to appreciate just how a determination by the FDA that the G.D. Searle & Co. experimental studies with aspartame were of an unacceptable quality in 1976 can be metamorphosed several years later into a view by that same Agency that essentially the same studies were sufficiently reliable for anyone to assess that this food additive is "reasonably certain" to be safe for consumption by humans.

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 revealed 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 at that time that only a portion of the observations on brain tumors had in fact been submitted 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 bodyweight 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 aspartame: 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 façade 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.

Sincerely yours

M. Adrian Gross,
Senior Science Advisor,
Benefits and Use Division,
Office of Pesticide Programs

I certify that the signature at left here is my own and that, to the best of my knowledge the contents of this letter are true and accurate.

Sworn and subscribed before me this 3rd day of November, 1987,