

Memorandum

Date May 19, 1981

From Robert J. Condon (HFV-105)

Subject Aspartame--Dissenting Opinion on the Brain Tumor Issue

To Joseph A. Levitt (GCF-1)

I do not concur that aspartame has been shown to be safe with respect to the induction of brain tumors. My opinion is based on following three reasons: (1) positive results seen in E33/34 for female rats; (2) problems in the conduct of E70 and E78; and (3) power of the studies.

E33/34

The correct statistical analysis of this study requires some adjustment of the observed incidence rate for the unequal mortality seen between the groups. The time-adjusted analysis demonstrates a significant ($P < .03-.04$) treatment effect, increasing rate of brain tumors with increasing dose levels. Comfort should not be taken in the lack of statistical significance of the point to point comparisons for the individual treatment levels because, for low spontaneous rates (1%), Fisher's Exact Test is extremely conservative. When the spontaneous rate is 1% and 50 animals per group are used, a nominal value of .05 for protection against false positive results is actually providing protection at the .00009 level of significance. Testing at the nominal level of .25 will result in an actual protection of .0546. Therefore care must be used in declaring results as being nonsignificant when a low spontaneous rate is present.

Additionally, there are some questions about the conduct of E33/34. Why were the phenylalanine blood levels significantly ($P < .05$) higher in the control males than in the high level treated males? In E70, liver phenylalanine hydroxylase activity was measured and found to be greater in the treated groups than in the control groups. The attached reference indicates that phenylalanine hydroxylase activity is suppressed when excess phenylalanine is added to the diet. If phenylalanine is being released from aspartame in the gut and absorbed, what is the explanation for the above results? Unfortunately I could not find where either study measured both phenylalanine in the blood and phenylalanine hydroxylase activity in the same study.

E70

In study E70 the rats were exposed in utero to aspartame and then fed aspartame in the diet. I have not been able to determine which animals were from which litters. All rats used from a litter would be on the same treatment level and, therefore, any treatment effect can not be separated from any effect due to the litters. Were all of the control animals with brain tumors from the same litter? This was an issue in one of our previous actions concerning one of the food dyes.

Also, there is a question of the identity and availability of the slides for review by UAREP. This same problem may also apply to E33/34 because EPL diagnosed two meningiomas in the high dose groups which were not reported as such by UAREP.

I do not believe that E70 eliminates concerns raised by E33/34.

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E78

Study E78 can not be used to resolve any concerns about aspartame itself. E78 was conducted using DKP a breakdown product of aspartame. E78 can be used to provide some additional information on the spontaneous rate.

E78 has a major defect that makes any conclusions from it of questionable value. There is no way to determine if the rats consumed the DKP and if they did, how much they actually consumed.

Also, how was the issue of uterine polyps raised by this study resolved?

Japanese Study

The Japanese study is too incomplete to conduct an appropriate review--the individual animal data are not available. This leads to problems evaluating effect such as reticulum cell sarcomas. I can not tell if the increase seen in the treated groups is due to multiple tumors in one rat or is a true treatment effect. Also, a dose related increase in kidney pelvic mineralization (kidney stones?) was observed in this study. It would be best not to base any conclusions on this study until full reports are available and can be thoroughly evaluated.

Conclusions on Studies

E33/34 suggestive or deficient depending on how the phenylalanine blood level decrease in the treated groups can be resolved in light of the effect of phenylalanine on the phenylalanine hydrolyase activity.

E70 incomplete or deficient depending of evaluation of litter effect and the issue of phenylalanine hydrolyase activity.

E78 deficient--do not know what dosage the rats actually received.

Japanese evaluation should await availability of data on the individual animals

What to do now?

This leads to the question of the power of the studies--what increase in a tumor rate could be detected and how often could it be detected? I believe that the agency should be at least as concerned about wrongly concluding a compound is safe (false negative rate) as it is about wrongly concluding a compound is harmful (false positive rate). If the agency tests for harmful effect using a 5% level of statistical significance, should not the agency also strive to be at least 95% confident that the compound is safe?

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