DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date May 19, 1981

From Staff Science Advisor, Office of Health Affairs (HFY-31)

Subject Aspartame: Review of Rat Tumor Issue

To Mr. Joseph A. Levitt (GCF-1)
Through: Director, Scientific Liaison Staff (HFY-31)

I have reviewed the information in the record of the Public Board of Inquiry hearing on the safety of aspartame. I have focused on the evidence relating to the questions whether aspartame is a brain carcinogen in experimental animals. In my view, the available evidence is limited and provides clear proof neither of the safety nor of lack of safety.

The Public Board of Inquiry reached essentially the same conclusion. They based their judgment on their evaluation of three studies which were designed to explore the potential of aspartame and its diketopiperazine to induce brain neoplasms in the rat.

The three carcinogenesis bioassays of aspartame and its diketopiperazine, hearing record documents E33/34, E70, and E78, have been reviewed and analyzed by the Bureau of Foods. Because in the past there have been questions regarding the authenticity of experimental results submitted by SEARLE, the authenticity of the results from the aspartame studies has been verified by the universities associated for research and education in pathology (URAEP). Although many logistic and technical discrepancies were noted in the URAEP review, the URAEP concluded that the data submitted by SEARLE, the aspartame sponsor, were authentic--meaning, I suppose, that experiments E33/34, E70, and E78 had indeed been done.

Detailed comparison of the pathology data submitted by SEARLE (both the original and subsequent pathology reports by Dr. Innes) and the URAEP review report shows wide variation in the reported spontaneous brain tumor incidence (see Tables I and II in 3/30/81 memo from Dr. Park to Mr. Levitt titled "Aspartame Issue Memorandum No. 1"). Although the original data sheets and protocols of the three studies were not available to me for review, I believe there is evidence that the studies would not meet the standards outlined in the GLPs. Further, it is my view that the deviations from GLP call in to serious question the reliability of the results of, and the conclusions drawn from, these studies by SEARLE and by the Bureau of Foods.

To me, the most troubling aspect of the three studies examined in the aggregate is the wide variation in the spontaneous rate of brain

tumors. It ranges from about 1% in E33/34 to more than 5% in E70. In my view, the true rate of spontaneous brain tumors in the rat is closer to 1% as suggested by the review of the data on 41,000 animals which shows an historical incidence of about .09%. Thus, I place greater weight on study E33/34, which is suggestive of a brain tumorigen effect at the least, relative to study E70 which is usually interpreted to be negative. Study E70 troubles me further for an additional reason: the relative distribution of the levels of phenylalanine and phenylalanine hydroxylase activity in the controls and treated animals. Viewed in the light shed by the data of Woods and McCormick (1964 Proceedings of the Society for Experimental Biology and Medicine, 116:427), to me such levels suggest that the control animals have been exposed to an unreported phenylalanine source.

Finally, some of the skepticism in the conclusions of the Public Board of Inquiry concerning the brain tumorigenic effect of aspartame was caused by the early appearance of brain tumors (gliomas) in the treated rats. It appears, however, that the time-to-tumor information available to the Board was inaccurate and that the accurate information would tend to diminish the Board's skepticism about the carcinogenic properties of aspartame.

For the preceding reasons, I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry I must recommend, therefore, that aspartame not be approved until additional studies are carried out using proper experimental designs.

Douglas L. Park, Ph.D.