



May 14, 2009

Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010 1001 I Street, 19th floor
Sacramento, California 95812-4010

JAMES A. SWENBERG, DVM, PhD

*Kenan Distinguished Professor, Environmental Sciences & Engineering
Director, Center for Environmental Health & Susceptibility
Director, Curriculum in Toxicology*

Re: Proposition 65 Listing of Aspartame

Dear Carcinogen Identification Committee:

This letter is regarding to your upcoming CIC meeting on May 29, 2009, that will prioritize 38 chemicals for possible preparation of hazard identification materials for future listing decisions. I noted that aspartame is one of the chemicals on your list and wanted to provide my perspective on the carcinogenicity data for aspartame. With great interest, I have followed this chemical for the last 30 years. I am a board certified veterinary pathologist, with many years of experience in chemical carcinogenicity research and bioassay evaluation, including spending 7 years on the NTP per review boards and being chairman of the NTP Board of Scientific Counselors. In addition, my Ph.D. research was on experimental neurooncogenesis.

As you are well aware, aspartame has been extensively studied for carcinogenic potential, having been evaluated in 5 rat carcinogenicity studies, 2 mouse carcinogenicity studies and 3 transgenic mouse carcinogenicity studies. Of these, only two demonstrated any evidence for carcinogenicity and both of these were conducted by the Ramazzini Foundation. None of the studies have shown an increase in brain tumors, including the new p16(INK4A)+/- transgenic mouse study conducted by the NTP. This model was selected due to its sensitivity to the induction of brain tumors.

The only issue related to carcinogenicity and aspartame has been the induction of lymphoma/ leukemia in the two Ramazzini studies, where increases were noted in the high dose groups, but the dose response was minimal. Hand selected slides from the first study were taken to the NTP for an informal peer review by board certified veterinary pathologists. Based on discussions with individuals on this review, more than half of the tissues were severely autolyzed, precluding an accurate diagnosis. There is a serious problem with studies conducted by the Ramazzini Foundation, in that they do not permit their studies to be peer reviewed, despite requests from the EPA, FDA and NTP. They also do not use current diagnostic criteria. Recently, the diagnosis of lymphoma/leukemia in these studies has been questioned, raising the

strong possibility that it is actually chronic infection by *Mycoplasma pulmonis*. This issue can be resolved by peer review and testing for *M. pulmonis*.

It would be a major step back in time to utilize data from recent studies that have not undergone a blinded peer review. It is high time that this common standard for quality control be required. The lack of such a requirement was part of the rationale for EFSA and the FDA to reject the conclusions of the Ramazzini studies. I urge the CIC to take a similar stand. It is totally unacceptable to conduct present day carcinogenicity bioassays using conventional rather than SPF animals, to not conduct blinded peer reviews of the histopathology and to have high percentages of the animals with autolysis that interferes with quality histopathology. In view of this, the Ramazzini studies should not influence the hazard identification of aspartame.

Thank you for taking your time to serve on this important decision.

Sincerely,

A handwritten signature in black ink, reading "James A. Swenberg". The signature is written in a cursive style with a large, sweeping initial 'J' and a long, trailing flourish at the end.