June 25, 2007

Dr. Andrew von Eschenbach
Commissioner, U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

An important new long-term animal feeding study, published in *Environmental Health Perspectives*, from the Cesare Maltoni Cancer Research Center at the European Ramazzini Foundation of Oncology and Environmental Sciences in Italy raises anew serious questions about the safety of the artificial sweetener aspartame.[1]

Dose-dependent increases in total malignant tumors, lymphomas/leukemias, and mammary carcinomas were observed in male and/or female rats. At the higher dosage level, the increases were statistically significant for lymphomas/leukemias in both male and female rats, mammary carcinomas in females, and tumor-bearing males. Non-significant increases were observed at the higher dosage for total tumors in males and females and for mammary carcinomas in males and at the lower dosage for total tumors in females, lymphomas/leukemias in males and females, and mammary carcinomas in females. Those non-significant increases would tend to elevate the dose-response trend.

The new study follows up on a study from the same laboratory, but is more sensitive because the rats were exposed to aspartame in utero; in the earlier study the rats were not fed aspartame until they were 8 weeks old. In the new study, groups of animals were exposed from the 12th day in utero to aspartame at levels of 0, 20, or 100 mg/kg bw/day (mg/kg) administered to the pregnant dams and, after weaning, to the animals through their feed. The previous study used those and several additional dosages (4; 500; 2,500; 5,000 mg/kg).[2] That study found statistically significant increased incidences of leukemias/lymphomas in both male and female rats, malignant schwannomas of peripheral nerves in males, and transitional cell carcinomas of the renal pelvis and ureter and their precursors (dysplasias) in females. Additionally, a few uncommonly occurring brain tumors occurred only in aspartame-treated animals.

The European Food Safety Authority (EFSA) reviewed the study and concluded for various reasons that aspartame was not demonstrated to be carcinogenic.[3] While EFSA's rationale may be debated, it must be reconsidered due to the results of the new study.

To put the doses used in the study in context, consider that the Acceptable Daily Intake of aspartame in the United States is 50 mg/kg. The 20 mg/kg dose is equivalent to a 50-

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[1] Soffritti M, et al. EHPonline.org (www.ehponline.org/members/2007/10271/10271.pdf, accessed June 13, 2007).
[2] Soffritti M, et al. Env Health Persp. 2006;114:379-85.
[3] Opinion of the Scientific Panel on Food Additives, Flavouring, Processing Aids and Materials in Contact with Food. The EFSA Journal. 2006;356:1-44.

pound child's drinking about 2½ cans of soda per day and a 150-pound adult's drinking about 7½ cans of soda per day (assuming 175 mg per 12-ounce serving of beverage[4]). The higher dose is equivalent to about 12½ and 37½ cans of soda per day.[5] The lower dose is something that about 5 percent of American teenagers actually consume.[6] Obviously, few people drink the larger amounts of aspartame-sweetened soda, but one must presume that lower levels of consumption would lead to increased, but proportionately lower, cancer risks. Of course, increasing exposure to aspartame is the fact that Americans are also consuming aspartame in powdered soft drinks, chewing gum, confections, gelatins, dessert mixes, puddings and fillings, frozen desserts, yogurt, tabletop sweeteners, and some pharmaceuticals such as vitamins and sugar-free cough drops.

In comparison to most animal toxicology studies, the new study has three significant strengths. First, it used more than the usual number of animals per sex/dosage group (95 controls and 70 in each group exposed to aspartame, as compared to the usual 50), thereby increasing the sensitivity of the study. Second, the animals were monitored until they died a natural death (as long as three years), as opposed to most studies, which are terminated after two years (104 weeks). Rats at two years of age are very roughly comparable to people at "retirement age," about 65, whereas three-year-old rats are more equivalent to people 80 to 90 years of age. Thus, the longer experiment sheds light on the effects of aspartame on "elderly" animals. Third, as noted above, the animals were exposed to aspartame during part of their fetal life (ideally, the dams would have been exposed to aspartame prior to pregnancy). In utero exposure reflects human experience and likely increases the sensitivity of the study.

We recognize that the FDA discounted the reliability of the first aspartame study on several grounds, particularly because the sponsor did not provide all the desired data.[7] Another reason was that transgenic mouse assays done by the National Toxicology Program did not identify problems. However, compared to such short- or medium-term assays and modes-of-action conjectures, chronic animal feeding studies are accepted widely as valid predictors of likely carcinogenic risks for humans: importantly, all acknowledged human carcinogens when tested adequately in animals are also carcinogenic, and many known human carcinogens were first discovered in animals. The FDA also noted that a recent large epidemiology study did not associate aspartame use with cancer. However, that study involved people who did not consume aspartame until they were over 50 years old, and measurement of aspartame consumption was imprecise. The present animal study is much stronger in those respects.

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[4] A Coca-Cola website indicates that a diet soda contains 175 mg of aspartame. (http://www.beverageinstitute.org/ingredients/pdf/Aspartame.pdf, accessed June 18, 2007) Other web sites indicate slightly different amounts.

[5] The quantities of soft drinks would be significantly lower if dosages were calculated on the basis of body surface, as some agencies do, instead of body weight.

[6] Jacobson M. Liquid Candy—Supplement (Center for Science in the Public Interest, 2005). (http://www.cspinet.org/new/pdf/liquid_candy_final_w_new_supplement.pdf, accessed June 18, 2007)

[7] FDA-CFSAN. FDA statement on European aspartame study. April 20, 2007. (http://www.cfsan.fda.gov/~lrd/fpaspar2.html, accessed June 19, 2007)

In light of the new aspartame study, which extends and corroborates the finding from an earlier study, we urge the FDA to immediately commence a careful review of the new study. Considering how widely aspartame in consumed by young children, as well as adults, in the United States and abroad, it is essential that this review be done as expeditiously as possible. If that review confirms that aspartame caused cancer in the laboratory animals, the FDA must invoke the "Delaney amendment" and revoke its approval for the artificial sweetener.[8]

Sincerely,

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[8] Food, Drug, and Cosmetic Act §409(c)(1)(3)(A).

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