



OCT 1 - 2014

Mrs. Betty L. Martini

(b) (6)

Re: Docket No. FDA-2002-P-0247 (formerly Docket No. 2002P-0317)

Dear Mrs. Martini:

This letter responds to your citizen petition dated July 16, 2002, requesting that the Food and Drug Administration (FDA) recall the food additive aspartame. You indicated that under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act), the FDA has the right to recall dangerous chemicals without a request from the manufacturer.¹ As explained below, FDA is denying your petition in accordance with 21 CFR 10.30(e)(3).

BACKGROUND

Section 409(d) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 348(d)) authorizes FDA to establish regulations prescribing, with respect to any particular use of a food additive, the conditions under which such additive may be safely used.

Under section 409(c)(3)(A) of the Act (21 U.S.C. 348(c)(3)(A)), the so-called “general safety clause” of the statute, a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. The concept of safety embodied in this requirement was explained in the legislative history of the Food Additives Amendment of 1958. “Safety requires proof of a reasonable certainty that no harm will result from a proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance.” H. Rept. 2284, 85th Cong., 2d Sess. 1 (1958). This concept of safety is incorporated in FDA’s food additive regulations (21 CFR 170.3(i)).

¹ The Bioterrorism Act did not provide FDA with mandatory recall authority for food. FDA was not given mandatory recall authority for food until the FDA Food Safety Modernization Act, which was signed into law on January 4, 2011 (sec. 206(a) of the Federal Food, Drug and Cosmetic Act). The FSMA recall authority states “If the Secretary determines, based on information gathered through the reportable food registry under section 417 or through any other means, that there is a reasonable probability that an article of food (other than infant formula) is adulterated under section 402 or misbranded under section 403(w) and the use of or exposure to such article will cause serious adverse health consequences or death to humans or animals, the Secretary shall provide the responsible party (as defined in section 417) with an opportunity to cease distribution and recall such article.”

The anticancer or Delaney Clause in section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 348(c)(3)(A)) provides that “...no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal....”

The food additive uses of aspartame are authorized under 21 CFR 172.804. The regulatory history, including FDA’s review of the safety of aspartame, is described in the Commissioner’s 1981 final decision (46 FR 38285, July 24, 1981) and in the 1996 final rule that replaced individually listed uses of aspartame with one regulation providing for the safe use of aspartame as a general purpose sweetener (61 FR 33654, June 28, 1996).

YOUR REQUEST

FDA concludes that your petition contains no substantive scientific evidence demonstrating that aspartame’s use presents a public health risk or that this sweetener is adulterated or misbranded under the Act. Moreover, the comments received in response to your citizen petition did not provide any information that has not previously been considered. Therefore, FDA is not aware of any scientific evidence that would change FDA's safety determination regarding aspartame.

The anecdotal accounts of adverse effects of aspartame cited in the citizen petition are not supported by scientific evidence. Many purported adverse effects (e.g. seizures and brain tumors) discussed in the citizen petition have been addressed in detail by FDA (46 FR 38285 at 38285 to 38308, July 24, 1981; and 48 FR 31377 at 31376 to 31382, July 8, 1983).

Since FDA approved aspartame, additional studies have been performed to further investigate adverse effects reported to be associated with the intake of aspartame. The FDA has reviewed a number of these studies including: (1) a series of studies conducted by the National Toxicology Program on the potential toxicity and carcinogenicity of aspartame in mice that were genetically modified to make them more susceptible to cancer, (2) a large epidemiology study (>500,000 people) sponsored by the National Cancer Institute that investigated whether there was any correlation between intake of aspartame and cancer, (3) a two year rat feeding study of aspartame and its decomposition product, 5-benzyl-3,6-dioxo-2-piperazine acetic acid, and (4) a long-term carcinogenicity study of aspartame in rats conducted by the European Ramazzini Foundation. FDA concluded that none of these studies provided evidence to alter FDA’s conclusion about the safety of aspartame.² Additionally, as part of FDA’s review of your petition, FDA performed a literature search of recent toxicological information on aspartame. The results of its search showed that there was no new information that would raise concerns regarding the safety of aspartame.

² Memorandum from D. Hattan, OFAS, CFSAN, FDA to L. Tarantino, OFAS, CFSAN, FDA. “Current Aspartame Safety Assessment Based on Evaluation of Recent Toxicological Data.” August 27, 2007.

In 1984, the Centers for Disease Control and Prevention (CDC) determined that the investigation of consumer complaints reporting symptoms associated with aspartame consumption did not identify any “specific constellation of symptoms clearly related to aspartame consumption;” the majority of frequently reported symptoms were “mild” and commonly seen in the general population; and the data did not provide evidence for the “existence of serious, widespread, adverse health consequences attendant to the use of aspartame.” <http://www.cdc.gov/mmwr/preview/mmwrhtml/00000426.htm>³

Over 100 toxicological and clinical studies were conducted to establish the safety of aspartame and demonstrated that aspartame is safe for use as a sweetener for the general population. Because phenylalanine is a component of aspartame, the FDA recognized that individuals with phenylketonuria must control their intake of phenylalanine and may need to either avoid or restrict their intake of foods and beverages that contain aspartame. Accordingly, for the safety of this segment of the population, FDA requires that all products containing aspartame include a statement specifically to alert phenylketonurics of the presence of phenylalanine.

FDA continues to monitor adverse reactions reported to be associated with the use of food additives and color additives, including aspartame. From January 1, 2004 through December 31, 2013, 195 reports of “adverse events” associated with consumption of aspartame or tabletop sweeteners such as Equal™ were submitted to the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS). Upon analysis of these data, FDA has not identified any causal link between aspartame consumption and the reported adverse events, and does not know of an established mechanism that would explain how aspartame is associated with the reported adverse events.

Since your citizen petition was filed with FDA, you have reiterated your concerns about the safety of aspartame in various communications to us. For the sake of efficiency, FDA is addressing the additional questions and concerns you raised in your February 25, 2011 email (which was in reply to FDA’s January 11, 2011 letter in response to your December 4, 2010 letter), as follows:

First, you questioned how aspartame can be suitable for use in food despite information on the Material Safety Data Sheet about methanol, a metabolite of aspartame. An MSDS (Material Safety Data Sheet) alone provides very limited information relevant to the safety evaluation or risk assessment of a given compound. Its primary purpose is to provide basic safety information on a material for those who will be handling or using the material, not from chronic intake of it. In the case of methanol from the consumption of aspartame, FDA assessed its safety from the results of toxicological testing on aspartame itself and from the estimated exposure to methanol resulting from the use of aspartame in food. Although aspartame ingestion results in the production of methanol, the levels formed from consumption of aspartame are small compared to that from consumption of other foods (*e.g.* apples or pears). FDA determined these levels to not be of toxicological concern, and is not aware of any information to the contrary.

³ Morbidity and Mortality Weekly Report November 2, 1984 33(43);605-7: Evaluation of Consumer Complaints Related to Aspartame Use.

Second, you asked if FDA was aware of “the severe toxic cumulative effect of free methanol in the body, building up over time (0-20 years) eventually causing organ, tissue and neurological damage.” FDA is not aware of any information that substantiates this claim as it relates to methanol exposure from the use of aspartame. From the data reviewed by FDA, methanol in aspartame (or in fruits and juices) does not accumulate in the body and is easily metabolized by the body’s metabolic capacities. One would have to be exposed to repeated doses of methanol at levels well above those resulting from consumption of aspartame-containing food products before any accumulation would occur.

As stated in previous FDA responses to you, FDA established an acceptable daily intake (ADI) for aspartame of 50 milligrams per kilogram of bodyweight per day (mg/kg bw/d) from the evaluation of safety information submitted in the food additive petition for the use of aspartame in carbonated beverages. In your letter dated March 21, 2011, you asked how the American ADI for aspartame could be higher than UK’s ADI. You also noted that the UK used a no observed adverse effect level (NOAEL) of 4000 mg/kg bw/day in rats to determine their ADI. The difference between the UK’s ADI and the American ADI (established by FDA) is due to two factors: 1) they are based on different studies and doses; and 2) they apply different safety factors. While the UK’s ADI is based on a NOAEL of 4000 mg/kg bw/day in rats, the American ADI is based on a no observed effect level (NOEL) of 200 mg/kg bw/day in humans. The 200 mg/kg bw/day NOEL in humans was based on detailed FDA scientific review of extensive clinical testing of different human subpopulations. Regarding safety factors, the UK applies a 100-fold safety factor, which yields an ADI of 40 mg/kg bw/day human consumption of aspartame. FDA originally applied the same 100-fold safety factor to an FDA established NOEL of 2000 mg/kg bw/day in rats, which yielded an ADI of 20 mg/kg bw/day. However, upon consideration of the reassuring results from a broad range of clinical studies which looked at the impact of aspartame consumption in humans, FDA had increased certainty about the safety of aspartame and applied a 4-fold safety factor to the NOEL of 200 mg/kg bw/day in humans, which yields the current American ADI of 50 mg/kg bw/day.

FDA has fully evaluated the safety related to dietary levels of methanol derived from aspartame and previously concluded that these levels do not represent uncommon or toxic levels of exposure. The American ADI of 50 mg/kg bw/day of aspartame (or 5 mg/kg body weight of methanol) results in between 20- and 160-times less methanol exposure than would result from the aspartame doses (1-8 gm/kg bw/day) the rats received. FDA has concluded that consumption of aspartame is well below the acceptable daily intake, that it is safe for its intended use, and that high levels of human aspartame intake are unlikely to exceed the ADI when it is used in food under current good manufacturing practice.

To date, no new credible evidence has been presented or discovered to alter FDA's original evaluation of the potential risk of methanol exposure from consumption of aspartame or of the established ADI for aspartame. Still, FDA continues to monitor

scientific literature for information that might indicate potential public health concerns with the use of aspartame as a food additive. FDA will take appropriate action if it finds that the food additive uses of aspartame provided for under 21 CFR 172.804 do not meet the safety standard for food additives.

In summary, the materials you submitted in support of your petition do not provide a basis for revoking the regulation pertaining to aspartame. Accordingly, for the reasons given above, FDA is denying your petition.

Sincerely,

(b) (6)

Steven Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition