

August 4, 2008

Dockets Management Branch (HFA-305) U.S. Food and Drug Administration 5630 Fishers Lane, Room 1061 Rockville, MD 20852

Office of Food Additive Safety Center for Food Safety and Applied Nutrition Food and Drug Administration 5100 Paint Branch Parkway College Park, MD 20740

Re: GRN No. 253 (and GRN No. 252)

Dear Sir or Madam:

Please consider the attached comment by UCLA toxicologists in your review of GRAS notification No. 253 for rebaudioside A purified from *Stevia rebaudiana* (Bertoni). The comment may also apply to notification No. 252 regarding a similar substance (we have submitted a FOIA request for the notification, but have not yet received the information). (Another company, Wisdom Natural Brands, has announced that it has self-affirmed a stevia derivative as GRAS.) The comment addresses the adequacy of testing done on rebaudioside A (and stevioside and steviol) and the results of the tests.

Rebaudioside A, if safe, could be a welcome substitute for the various artificial sweeteners, such as saccharin, aspartame, and acesulfame-K, that have been the foci of great controversy, because of (inconclusive) evidence of potential carcinogen risk. Older studies on cruder extracts of stevia indicated potential toxic effects on reproduction in rats and hamsters. The newer tests did not find similar problems with the purer rebaudioside A preparation. However, importantly, several *in vitro* and *in vivo* genotoxicity tests of steviol and stevioside, which are closely related to rebaudioside A, found substance-related mutations, chromosome aberrations, and DNA breakage. Such findings indicate that rebaudioside A might cause similar problems, or cancer, in humans.

In addition, a high-potency sweetener like rebaudioside A will probably be consumed in significant quantity by tens of millions of people. The FDA's testing guidelines (Redbook II) for

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¹ Yamada A, Ohgaki S, Noda T, et al. Chronic toxicity study of dietary Stevia extracts in F344 rats. J. Food Hyg. Soc. Japan 1985;126:169-83 (Abstract in English. Partial English translation provided); Wasuntarawat C, Temcharoen P, Toskulkao C, et al. Drug Chem. Toxicol. 1998;21:207-22.

food additives consumed in significant quantity indicates that, as a basic safeguard, companies should conduct chronic feeding studies of such substances in two rodent species, typically rats and mice. GRAS notification No. 253 indicates that rebaudioside A has been tested in only one species (rat). In the present case, the need for a lifetime² feeding study in a second species (mouse) is underscored by the positive findings in multiple genotoxicity studies.

Furthermore, because of differences in pharmacokinetics of stevioside and rebaudioside A, certain toxicity tests (such as carcinogenicity studies) involving stevioside may not be predictive for rebaudioside A. Rebaudioside A is the ingredient that would be used in food, and that is the ingredient that should be used in tests.

Considering the genotoxic effects of rebaudioside A and the absence of a lifetime feeding study in mice, and considering that impartial toxicologists from UCLA (in contrast to the paid consultants to Cargill³) are criticizing the testing and safety of rebaudioside A, *this ingredient cannot be considered generally recognized as safe*.

We urge the FDA to advise the sponsor(s) that they should submit a full food additive petition, including the results of a new chronic feeding study on mice and repeats of all the genotoxicity tests. The food additive route would enable the FDA to review the safety tests in detail, rather than give them the more perfunctory examination characteristic of GRAS reviews. Furthermore, to obtain objective tests of this potentially widely used substance, the FDA should ask the National Toxicology Program to conduct chronic feeding studies on rats and mice, as well as a battery of genotoxicity tests (including repetitions of both the positive and negative studies conducted by the notifier, as well as other tests deemed appropriate).

Sincerely,

Michael F. Jacobson, Ph.D.

disclose their conflicts of interest.

Michael F. Jacobson

Executive Director

² Any new "lifetime" study should be not 80 or 104 weeks, but closer to 2.5 years, the actual "lifetime" of a mouse (http://sageke.sciencemag.org/cgi/content/full/2003/25/as1). Huff J, Jacobson MF, Davis DL. 2008. The limits of 2-Year Bioassay Exposure Regimens for Identifying Chemical Carcinogens. Environ Health Perspect: doi:10.1289/ehp.10716. [Online 30 June 2008] http://ehp.niehs.nih.gov/docs/2008/10716/abstract.html
³ The FDA should require GRAS notifiers to disclose financial conflicts of interest of members of their GRAS panels, just as medical journals, federal advisory committees, and others require authors, nominees, or members to