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June 3, 2013

Mr. Michael M. Landa, J.D., Director
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Dear Mr. Landa:

Extracts of the leaves from the *Ginkgo biloba* tree ("Ginkgo") are widely used in dietary supplements, both in single-ingredient pills made by Natrol, GNC, Solaray, Now, Nature's Way, Ginsana, and others, and in combination with other ingredients in products such as Bayer One-A-Day Women's 50 Plus Advantage multivitamins. They are also used in some energy drinks, such as several Rockstar varieties, Hansen's Energy Pro, Guru, and Steven Seagal's Lightning Bolt. Yogi Tea's Ginkgo Clarity has Ginkgo, and Redco Foods adds ginkgo to its Salada "Brain Boost" green tea. Companies portray Ginkgo as a substance that improves memory or concentration, but there is little supportive evidence.[1]

Claims regarding Ginkgo's *supposed* health benefits ("memory" and "supports cognitive function") are false and should be stopped, but Ginkgo hasn't been thought to pose a serious health risk. That changed in March 2013 when the National Toxicology Program ("NTP") of the National Institute for Environmental Health Sciences released the results of animal studies in which *Ginkgo biloba* extracts caused cancer.

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[1] "The evidence that *Ginkgo biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable." Cochrane Database Syst Rev. 2009 Jan 21;(1):CD003120. doi: 10.1002/14651858.CD003120.pub3. Ginkgo biloba for cognitive impairment and dementia. Birks J, Grimley Evans J. http://www.ncbi.nlm.nih.gov/pubmed/19160216

Also, "(W)e have found no convincing evidence from randomised clinical trials for a robust positive effect of G. biloba ingestion upon any aspect of cognitive function in healthy young people, after either acute or longer term administration." Hum Psychopharmacol. 2007 Jul;22(5):265-78. Ginkgo biloba is not a smart drug: an updated systematic review of randomised clinical trials testing the nootropic effects of G. biloba extracts in healthy people. Canter PH, Ernst E. http://www.ncbi.nlm.nih.gov/pubmed/17480002

The NTP studies found "clear evidence" that Ginkgo caused liver cancer in male and female mice and "some evidence" that Ginkgo caused thyroid cancer in male and female rats.[2] In the high-dose groups of mice, the ingredient was no borderline carcinogen: it caused hepatocellular carcinomas in 94 percent of male mice (compared to 44 percent of the controls) and 96 percent of female mice (compared to 34 percent of the controls). The ingredient may also have caused other tumors as well. "In some instances, the number of cancers exceeded the numbers ever seen in mice in the lab, the investigators" told *The New York Times*.[3]

On the basis of the NTP studies, the FDA Seattle District office has already sent a warning letter to advise a beverage maker that one of its products is adulterated (and also misbranded for other reasons). On March 28, 2013, the FDA told Stewart Brothers, Inc., which makes SuperBerry Fruit Juice Drink Blend, that it knew of no basis for considering Ginkgo to be Generally Recognized As Safe ("GRAS"), especially in light of the NTP studies.[4] On May 23, 2012, even before there was evidence that Ginkgo caused cancer, the FDA's New Orleans district office in Nashville, Tennessee, told Rockstar, Inc., that its Roasted Coffee & Energy products were adulterated because they contained the herbal ingredient:[5]

> Any substance added to a conventional food, such as your Rockstar coffee products, must be used in accordance with a food additive regulation, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts for its use in foods [21 CFR 170.30(g)]. There is no food additive regulation which authorizes the use of Ginkgo. We are not aware of any information to indicate Ginkgo is the subject of a prior sanction [see 21 CFR 181]. As explained below, we are not aware of any basis to conclude that Ginkgo is GRAS for use in conventional foods.

We urge the FDA to take actions to protect consumers from this herbal ingredient that causes cancer in animals and presumably in people. Specifically, we ask the FDA to:

- Inform the food industry that Ginkgo is not GRAS, prior sanctioned, or an approved food additive and may not be used in any food. The FDA should give companies a reasonable time, such as 30 days, to recall their products from the marketplace, after which time it should seize any remaining products.

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[2] NTP technical report on the toxicology and carcinogenesis studies of *Ginkgo biloba* extract (CAS no. 90045-36-6) in F344/N rats and B6C3F1/N mice. March 2013. NTP TR 578. NIH Publication No. 13-5920.
[3] http://well.blogs.nytimes.com/2013/04/29/new-doubts-about-ginkgo-biloba/
[4] FDA Warning Letter SEA 13-15. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm346316.htm; accessed April 26, 2013.
[5] FDA Warning Letter 2012-NOL-22. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm309080.htm; accessed April 26, 2013.

- Inform the dietary supplement industry that Ginkgo poses a substantial and unreasonable risk to consumers, provides no benefit to consumers, and must be removed from the market within a specified period of time.[6] FDA should take legal action if companies fail to stop marketing all of their products that contain Ginkgo.

The American Botanical Council has argued that the NTP used an extract of *Ginkgo biloba* that is not representative of Ginkgo supplements sold in the United States.[7] The Council claimed that the concentrations of three important constituents (flavonol glycosides, terpene lactones, and ginkgolic acids) of Ginkgo were significantly different in the NTP product from what is generally available in the marketplace. But the NTP maintains that the composition of the extract it tested falls within the range of what is available in the marketplace. Hence, the prudent course of action would be for the FDA to ensure that all products that contain extracts of *Ginkgo biloba* are removed from the marketplace.

Sincerely,

Michael F. Jacobson, Ph.D.
Executive Director

David Schardt
Senior Nutritionist

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[6] The standard for removing a dietary supplement from the marketplace was established in an appellate court's decision in a case involving ephedrine alkaloid dietary supplements ("EDS"). The court ruled that:

> In determining that EDS pose an "unreasonable risk of illness or injury," the FDA found that the weight loss and other health benefits possible from the use of EDS were dwarfed by the potential long-term harm to the user's cardiovascular system. The agency went on to enact a complete ban on the product after making a finding that any amount of EDS had negative ramifications on the cardiovascular system and, based on the FDA's analysis, EDS provided no benefits so great as to justify such risk.

In the present case, supplements containing *Ginkgo biloba* pose a risk of cancer to consumers, and that risk is not balanced by any demonstrated health benefits.
Appeal from the United States District Court for the District of Utah (D.C. No. 2:04-CV-00409-TC). http://www.casewatch.org/fda/court/ephedra/utah2.shtml; accessed April 26, 2013.

[7] http://ntp.niehs.nih.gov/NTP/About_NTP/TRPanel/2012/February/PublicComm/Blumenthal20120125.pdf