Dear Dr. Jacobson,

Bruce forwarded me your email to him since my division deals with regulatory testing. As you know, we strenuously object to your call for additional animal testing since the toxicity of stevia glycosides has been thoroughly characterized. *Stevia rebaudiana* has been used for sweetening beverages and foods for more than 400 years, and more than 750 tons of stevia leaves per year are currently used as crude extract for consumption. Countries that allow the use of steviol glycosides include Japan, China, Russia, Korea, Brazil, Paraguay, Argentina, Indonesia and Israel. Further:

- At its sixty-ninth meeting in June 2008, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a permanent acceptable daily intake (ADI) of 0–4 mg/kg bw;
- JECFA noted that the results of the new studies showed no adverse effects of steviol glycosides when taken at doses of about 4 mg/kg bw per day for up to 16 weeks by individuals with type 2 diabetes mellitus and individuals with normal or low-normal blood pressure for 4 weeks;
- In August 2008, Food Standards Australia New Zealand (FSANZ) concluded that there are no public health or safety concerns for steviol glycosides when used as a food additive, paving the way for products sweetened with them to enter the Australian market.

CSPI has failed to convincingly challenge the claim that rebaudioside A is generally recognized to be safe among qualified experts. In fact, the report upon which you based your claim for additional animal testing (a report prepared for CSPI) ignores relevant information, presents flawed arguments, overlooks the conclusions of authors they themselves cite as well as relevant scientific criticism, and misreports data. Just a few examples include:

- With regard to the potential genotoxicity of stevioside, Kobylewski and Eckhert cite the *in vitro* mutagenicity study (an Ames test) of Suttajit et al. (1993). They fail to mention the authors’ conclusions that stevioside “is not a mutagen toward bacterial cells or a genotoxin to cultured mammalian cells, and it is not carcinogenic to experimental animals either” since “[o]nly at an unusually high dose, 50 mg/plate, was stevioside mutagenic to TA98 but not to TA100” and “[t]he mutagenicity might be due to some impurities in the sample.” The only other study cited in support of stevioside’s potential genotoxicity is a comet assay conducted by Nunes et al. (2007). This study prompted letters by Gary M. Williams, M.D., New York Medical College and Jan M.C. Geuns, Catholic University of Leuven which raised numerous concerns.

- With regard to differences in pharmacokinetics between rebaudioside A and stevioside, Kobylewski and Eckhert claim there was a lower C_{max} of steviol glucuronide and steviol with rebaudioside A compared to stevioside when the tables they themselves reproduce clearly show a higher C_{max} for steviol (227 vs. 121ng/mL). Also, Wheeler et al. (2008) draw their conclusions from the geometric mean C_{max} values (1472 ng/mL for rebaudioside A and 1886 ng/mL for stevioside) and the geometric mean AUC_{0–t} values (30,788 ng h/mL for rebaudioside A and 34,090 ng...
h/mL for 34,090 ng h/mL) presented in a table that Kobylewski and Eckhert omitted. These values correspond to differences of 22 percent and 9.7 percent, respectively. Wheeler et al. state that "on the basis of the similarity in human metabolism to the primary metabolite steviol glucuronide following administration of rebaudioside A or stevioside…, it can be concluded that previous human studies and rodent toxicological studies conducted with stevioside are relevant for assessing the human safety of rebaudioside A."

- With regard to the observation that bioassays of chemicals that did not find carcinogenicity in rats did find carcinogenicity in mice, Kobylewski and Eckhert state that NTP found no evidence of carcinogenicity in rats for 1,3-butadiene – the only one of their examples that NTP lists in its 11th Report on Carcinogens (RoC) as a known human carcinogen. NTP did not test 1,3-butadiene in rats.

Sincerely,

Jessica Sandler
Director, Regulatory Testing Division
People for the Ethical Treatment of Animals
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"No one may permit any preventable pain to be inflicted on animals, even though the responsibility for that pain is not ours. No one may appease his conscience by thinking that he would be interfering in something that does not concern him. No one may shut his eyes and think the pain, which is therefore not visible to him, is non-existent." -- Albert Schweitzer

In these difficult times, please remember the animals. Donate today.