LETTER TO THE EDITOR

Stevia: It's Not Just About Calories

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To the Editor:

The recent review of Stevia [1] contributes to furthering the scientific database of stevia (leaf and extract), steviol glycosides, and steviol and their applications in food and beverages. The article discussed these compounds in relation to perceived pharmacological activity, their potential use as therapeutic agents, and available toxicological and clinical evidence to support safety. While the overall conclusions that steviol glycosides specifically are safe for use in food applications are appropriate, the authors did not adequately differentiate between the results of studies relating to the toxicological, biochemical and pharmacological profiles of uncharacterized stevioside/steviol glycoside preparations (e.g., stevia leaf extracts or stevia leaf preparations) and those from studies conducted on purified preparations of stevioside/steviol glycosides and steviol. Also, the authors cited the conclusions of regulatory authorities with respect to characterized preparations of steviol glycosides to support the safety of stevia extracts/leaf preparations. Finally, the authors do not include the latest positions of regulatory authorities regarding human safety of steviol glycosides.

The article presents a summary of a number of biochemical studies to document the effects of stevia extracts/stevia leaf preparations on glucose homeostasis, blood pressure regulation, antioxidant status, immune system responses, and inflammatory bowel disease. These studies are not relevant to the pharmacological profile of specific purified steviol glycosides (e.g., stevioside, rebaudioside A) since it is well established that some stevia extracts are crude mixtures that contain multiple components of the stevia leaf, including those components that do not provide a sweet taste. These mixtures also vary considerably in quality, purity and composition. Therefore, it is unclear whether the presence of a non-glycoside substance(s) in these mixtures might be responsible for any observed pharmacological activity or whether the study design itself may have contributed to some of the reported findings. Moreover, the in vitro studies are not relevant to the safety of steviol glycosides consumed orally since steviol glycosides are hydrolyzed completely by the gut microflora to steviol prior to absorption, with no systemic absorption of the aglycone form (i.e., the form used in the *in vitro* studies).

In contrast to studies conducted with less pure steviol glycoside preparations, studies conducted with purified preparations do not indicate any evidence of pharmacological effects. For example, a peer-reviewed clinical study of high statistical power [2], not cited by the authors [1], demonstrated that highly purified rebaudioside A at doses of up to 1000 mg/day had no effect on glucose regulation. Likewise, a similar well controlled peer-reviewed study on a highly purified rebaudioside A preparation (doses of up to 1000 mg/day) showed a lack of an effect on blood pressure regulation [3]. While stevia extracts, leaf preparations, or the glycone form of individual steviol glycosides (*in vitro*) may have limited pharmacological activity, there is no evidence to indicate pharmacological effects of steviol glycosides *in vivo*.

To support the safety of stevia leaf extracts, the authors [1] present summary results of a number of toxicology studies in their section entitled "Stevia is Safe and Non-Toxic". While 3 of the studies mentioned pertain to stevia leaf extract, the vast majority (15 studies) were conducted specifically on stevioside, rebaudioside A, or steviol. One must be cautious when extrapolating the results of studies on specific steviol glycosides to the assessment of the safety of stevia leaf extract since, as discussed, these extracts contain numerous other substances beyond the specific steviol glycosides evaluated in the studies cited.

In addition to the studies on specific steviol glycosides, the authors [1] also cite the conclusions of JECFA, AFSSA, and the FDA that pertain to these substances to infer similar conclusions on the safety of stevia leaf extract. These regulatory authorities have not concluded that stevia leaf extract *per se* is safe. Their evaluations focused on the purified steviol glycosides having well defined chemical specifications. Specifications established by the JECFA for steviol glycoside preparations [4] state that these must contain a minimum of 95% total of the named steviol glycosides with the predominant steviol glycoside components being stevioside and rebaudioside A.

The author's interpretations of the safety opinions of regulatory authorities are also incomplete. Although the authors cite one JECFA review (JECFA 2006) in their analysis, the favorable 2008 JECFA review [5] which estab-

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lished the safety of and a permanent ADI (0-4 mg/kg body weight/day) for steviol glycosides was omitted as was the 2010 favorable review by EFSA [6] which concluded that steviol glycosides, complying with JECFA specifications, are not carcinogenic, genotoxic or associated with any reproductive/developmental toxicity.

These latest reviews by JECFA and EFSA included an analysis of the most recent data on steviol glycosides, including studies demonstrating a lack of reproductive toxicity, and studies demonstrating no effects on either blood glucose hemostasis in people with Type 2 diabetes or on any hemodynamic parameters in normotensive or hypotensive individuals. In addition to the FDA GRAS Notification cited by the authors for rebaudioside A, there have been 10 other FDA GRAS Notifications for purified rebaudioside A, stevioside or steviol glycoside preparations composed primarily of rebaudioside A and stevioside which the FDA has accepted as GRAS for use in foods [7]: (http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing&page=1).

It should also be noted that in addition to approvals in Brazil, Korea, Japan and France (for rebaudioside A) cited by the authors, countries where official approval for steviol glycoside preparations meeting JECFA specifications for use in foods and beverages include: China, Taiwan, Malaysia, Australia, New Zealand, Argentina, Paraguay, Uruguay, Mexico, Peru, Colombia, Russia/Ukraine and Turkey.

In summary, Thomas and Glade [1] quite correctly assert the safety of steviol glycosides, however, these authors have extrapolated the results of studies and regulatory opinions on well characterized steviol glycoside preparations to inappropriately support the safety of stevia leaf/stevia leaf extracts. In addition, the authors did not adequately differentiate reported pharmacological activity of crude stevia extracts, or of steviol glycosides when tested *in vitro*, from the demonstrated lack of activity of steviol glycosides *in vivo*. Finally, the authors did not include the most recent conclusions of regulatory authorities on the safety of well characterized steviol glycosides.

CONFLICT OF INTEREST STATEMENT

Drs. Tarka and Roberts provided consulting services to Cargill, Inc. on the toxicology and safety of steviol glycosides including responding to this publication. There is no statement in the paper by Thomson and Glade (2010) regarding a conflict of interest nor is the source of funding for that review identified.

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