Reviewer's report

Title: A systematic review on the effect of sweeteners on glycemic response and clinically relevant outcomes

Version: 1 Date: 7 July 2011

Reviewer: rejeanne gougeon

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This manuscript evaluates the effectiveness of intense sweeteners in controlling weight and minimizing risk factors for complications associated with obesity and type 2 diabetes by performing a systematic review and a network meta-analysis of eligible randomized clinical trials. The authors conclude from their review that little high-quality clinical research has been done to assess long term risk/benefit of non-caloric sweeteners considering their frequent consumption for weight and glycemic control. Still, despite the limited available studies, this review suggests that the evidence for a vital role for non-caloric sweeteners in an effective adult population health strategy for prevention of obesity and related co-morbidities is poor. Latest research news (albeit non-peer reviewed) show positive relationships between diet soft-drink consumption over 9 years and change in the waistlines of elderly, after adjustment for confounders and increased blood glucose with heavy aspartame exposure in diabetes-prone mice. Thus, this paper is highly pertinent in reviewing the evidence for clinically relevant outcomes from sweetener consumption to provide balance from risk and safety assessment studies, and to recognize that substituting or decreasing added sugars is healthful. This review demonstrates that adequately powered RCTs are needed to obtain a more balanced systematic risk/benefit analysis in order to better define recommendations and provide comprehensive advice to policy-makers and consumers regarding sweeteners. The review is extensive; the criteria for selection of studies and the statistical methods used are appropriate and well described but do require careful reading, particularly tables 3 to 6.

Discretionary Revisions: It would be of interest to discuss 1) the absence of brain and pancreatic responses with intense sweeteners vs. with sugar; 2) the ambiguous psychobiological signals with intense sweeteners that may confuse the body’s regulatory mechanisms leading to a loss of control over appetite and overeating; 3) that intense sweeteners are not appetite suppressants and fail to reduce motivation to eat.

Minor essential revisions:

Page 13, line 17-19: terms ADI and CPG recommendations need clarification; Acceptable daily intake (ADI) of sweeteners are defined as safe amounts per kg body weight such that reducing energy intake would not change its value. However for sucrose and fructose, there are no ADI but Clinical Practice Guidelines’ recommendations of 10% of energy such that intakes of 60
grams/day could exceed 10% with energy restriction but not necessarily a concern for safety except displacing nutritious foods.

Page 15 line 3-8: text should follow the same order as in the table (general before overweight)

Page 15 line 10 and 11: should specify that the study in ref 61 is in participants with type 1 diabetes.

Tables 3 to 6: explanations given with table 3 could be repeated under tables 4 to 6 for clarity such that each table stands on its own.

The discussion is well balanced and conclusions are supported by the results obtained. The authors could mention also the lack of good data to determine, if sugar is displaced by intense sweeteners, whether there is incomplete compensation from other foods, a necessity if long term benefits are to be achieved. This review is limited to adult population and the conclusions may not be applied to sub-populations such as high soda consuming adolescents who could be better responders to intense sweeteners.

The manuscript needs some language corrections before being published: abbreviation for kilocalories is kcal (low case c); conclusions in abstract: first word: use considering instead of despite; 2nd line of conclusions …..in this condition; diabetics (p. 10) and diabetic patient should be replaced by diabetic people or individuals or participants; p. 8 line 1 : oral antihyperglycemic agents; in discussion page 17, line 11: control group was asked; page 18, line 19: whether substituting a non-caloric; page 19, line 1: delete the second consumed; line 5: most importantly; line 13: improvements in the health of the population; page 20 line 3: will improve public health.

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests