Author’s response to reviews

Title: Review of the nutritional benefits and risks related to intense sweeteners

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Version: 2
Date: 29 May 2015

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Response to reviewers – article EI

Reviewer 1:

General comments
The paper is well written and elaborated. The discussion is clear and of good scientific quality.

Authors: We thank the reviewer for these positive comments on our manuscript.

Major Revisions
1. The paper is referring to the nutritional benefits but also to the risks. An Acceptable Daily Intake (ADI) has been established for the sweeteners discussed in the paper. However, in risk assessment of additives, the concept of ADI is quite important. The authors failed in addressing this aspect in the review.

Authors: This is an important point raised by the reviewer. We now discuss this point in the discussion section of the revised ms.

Minor Revisions
2. [Methods p4, 1st paragraph] It is advisable to make reference to the EU regulations concerning the authorisation of sweeteners. According to the regulation EU 1131/2011 steviol glycosides are authorised and rebauside A should be replaced with steviol glycosides in the text.

Authors: We agree with the reviewer and we have changed our manuscript accordingly.

3. [Effects on body weight and consumption, p7 line 14] references to the several original articles is missing

Authors: We thank the reviewer and we have updated our references.

Reviewer 2:
This is a very timely and interesting article, since, with growing interest in the health effects of sucrose and fructose intake increasing, attention turns to whether intense, low energy, sweeteners may be endorsed or promoted as a public health intervention.

Authors: We thank the reviewer for this kind comment.

Major compulsory revisions.
1. Although a lot of material is presented and described, I felt that it could be better organised. I felt that meta-analysis results were often interpreted or labelled inconclusive without giving the reader an overview of the criteria used to select studies, what the comparison groups are, and what the pooled effect was, if one was reported. I would favour that major meta-analyses or trials referred to in the text be summarised in table form, enabling the reader to determine what (1) what was the population under study, (2) what was the nature of the studies included (observational or RCT), (3) the nature of the comparison (eg. dose or dietary intake, which sweetener or sweeteners?), and (4) the magnitude of the effect & (5) an assessment of whether or not there is between study heterogeneity (for meta-analyses only). I believe this would help the reader assess the nature and consistency of the evidence (or lack of it) in a more concise and accurate way.

Authors: This is an important point that has been exhaustively discussed when writing the first draft of our manuscript. Unfortunately, with the huge number of studies (i.e. more than 100 cohort, case control or RCT studies) analysed in this review, it is impossible to put all of them in a table. However, we have added a table summarizing the results and the methodology and the two main meta-analyses.

2. The authors also conclude in several sections that there is 'insufficient evidence' to determine whether there is adverse or beneficial effects of IS on
various health outcomes. It would be helpful if the authors stated what their criteria are for determining whether there is 'sufficient evidence' for adverse or beneficial effects. It seems that one can always say 'there is insufficient evidence', but without addressing what would be needed for the authors to be convinced, it seems hard to interpret these statements.

Authors: We fully agree with the reviewer that our methodology was not clear. We have added this paragraph in the method section: “Whatever its design and quality, a single study is never able to establish the causality between the exposure and the disease, in this case between IS consumption and its effects on health. In our review, we used part of Hill’s criteria of causation to assist in the assessment of the causal relationships. Indeed, a modified version of the Bradford Hill criteria was used to evaluate the evidence of a causal relationship between IS consumption and health outcomes. As a matter of fact, the following eight criteria, considered as the most important to answer our questions, were used in our review: strength, consistency, temporality, coherence, experiment, plausibility, analogy and biological gradient. One criterion, the specificity, was omitted because considered as nonspecific to our various outcomes. It should be pointed that none of these criteria alone is sufficient to establish causality and that no systematic algorithm was used. The final interpretation of the causality was based on experts’ judgment based on all analysed data. “

3. In some statements relating to measures of effect, it is not made clear what two groups the effect measure is comparing.

Authors: We have modified part of the text accordingly.

Minor Essential Revisions

4. In the section of "effects on body weight and composition", there is a reference that appears incomplete (“and several original articles (ref ...)").

Authors: We have updated our references.