Reviewer’s report

Title: EFSA’s toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives?

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Reviewer: Michael Kundi

Reviewer’s report:

Millstone & Dawson review EFSA's most recent assessment of the toxicity of aspartame from 2013. The review finds evidence for a not balanced assessment of the evidence by dismissing positive findings based on a much stricter set of criteria than applied for negative findings for which the panel was more tolerant. Authors must be applauded for their detailed and thorough analysis of the EFSA panel's report. While the evidence does not speak for itself and therefore must be interpreted by individuals with sufficient experience in the relevant field of science and while it must be appreciated that value judgements are unavoidable, it is nevertheless of utmost importance that this process of evaluation is transparent and balanced. Unfortunately this is not always the case and especially if strong commercial, governmental, or military interests are involved, assessment of evidence tends to deviate from these requirements. Rigid application of criteria of selection of panel members is not always feasible because in an era when public funding of science is strongly decreasing, scientist with sufficient experience in a certain area might have all at one time or other received funding from the industry. In my view this does not necessarily cause a conflict of interest as long as a rigorous assessment is applied without distinction of the direction in which the evidence points. Transparency and possibly publicness, as favored by the authors, could be instrumental for this goal.

The first author is well-known for his stance in the controversy about the potential hazards of aspartame and, because of the billion Euro/dollar business that lies behind its marketing and continued widespread use, I am inclined to make allowances concerning phrasing of important statements. But when they get too bitter or emotional I recommend revision as detailed below.

The labeling of the categories C1 to C7 is not reader-friendly. I suggest changing this to: rP for reliably positive, uP for unreliably positive, and rN, uN analogously for negative studies. C for contradictory. ELlow and ELhigh can be the abbreviation for C6 and C7, respectively.

I do not agree with the statement in the Abstract and in the text that "If the panel had been even-handed, the proportions deemed reliable and unreliable should be similar when comparing between studies with prima facie evidence of harm and those providing no such evidence". While the huge disproportion in these percentages that is present in EFSA's assessment is suggestive of bias, these percentages should be equal only of positive and negative studies are equally reliable, which need not be the case. Therefore, this statement must be replaced. What can be stated is that if the panel had been even-handed, the criteria for assessing reliability must have been equal for positive and negative studies.
p.6, 1st paragraph: Do not use terms like 'brush under'.

p.12/13: The sentence citing what Rumsfeld might have or not have said should be deleted. The facts speak for themselves.

p.23, 1st paragraph: The sentence: 'The units in terms…' can be deleted as this has been defined previously (p.17/18).

p.23, 2nd paragraph: Specification of an ADI as 'one hundredth of the NOAEL' is not correct. The subsequent explanations are correct; therefore this sentence should be removed.

p.27: The definition of the 'Contradictory' category is elusive. It is unclear whether it concerns reliability or positivity. Please clarify!

Table 2: I suggest reconstructing this table. First, since the columns already indicate the category, the labels C1 etc. are not needed. Furthermore, it would be much more relevant to have only two lines (positive and negative studies) but three categories: reliable, unreliable, contradictory.

Table 3: Why is the term 'estimated' used?

p.40/41: There are several epidemiological studies that the panel dismissed due to the possibility of residual confounding. While this sounds as a rational argument, it is in fact not a scientific statement but an immunization strategy to maintain the zero hypothesis. A scientific statement is characterized by its ability to be falsified by a finite series of tests. But for such a statement this is not possible, because whatever you do to account for confounding it can always be claimed that there is a possibility of residual confounding. Furthermore, the study of Englund-Ögge does not contradict the study by Halldorsson. In fact, both studies found indications of risk at increasing levels of use of artificially sweetened soft-drinks.

The studies included in the Appendix table should have a reference list.

Minor errors:

Consistently use capitalization of aspartame (I prefer it being not capitalized).

Do not report daily doses as 'mgs/kg bw/day' but 'mg/kg bw/day'

Abstract, Conclusions, line before last: Omit 'while'

Header of Table 1: Change 'using' by 'used'

p.33, 2nd paragraph: Use 'developmental'

p.37, 2nd paragraph: Closing apostrophe missing after 'robust'
There are many spelling errors in the Appendix table. These will be easily shown if the check grammar feature is invoked.

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