Reviewer’s report

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

Version: 0 Date: 11 Mar 2019

Reviewer: Olwenn Martin

Reviewer’s report:

Dear authors,

I read this thought-provoking manuscript and substantial amount of analysis presented in the appendices with great interest. Having digested this large amount of material, there are a number of remaining questions that, if addressed, I believe should improve the clarity of the manuscript for a reader not familiar with the substance or events related with its evaluation.

Section 1 makes for a compelling narrative of regulatory capture by private interests. Some of the evidence alluded to is referenced to books published on this specific matter. For transparency, I would recommend replacing secondary sources by the primary sources originally referenced in the books cited. A reader is left unable to verify claims independently without owning copies of these books. Ideally, if some of these material are made publicly available, a web link to sources would allow readers to access the evidence directly but I understand that this may not always possible. At least some indication of how these insights in political processes were gleaned would allow the reader freedom to exercise their critical judgment. As way of example, I'll refer to reference 29 on page 12, where it is claimed that Searle's former CEO was offered a job as ambassador in Beirut in exchange for a promise to get aspartame on the market. Without a copy of Cockburn's book, it is difficult to gauge how these serious allegations were established.

Section 2 describes the methodology for the analysis of EFSA ANS panel appraisal of the evidence. The null hypothesis of symmetry is clearly stated but it should be qualified by the fact that symmetry cannot be derived simply from the number of positive and negative studies deemed reliable and unreliable. It depends on the truth regarding the safety or otherwise of aspartame which one can only guess at, with one's own set of conscious or subconscious biases. In a situation where the truth would be that aspartame were safe, then a situation whereby all positives would be unreliable is envisagable (discounting the fact that we would expect some reliable positive to occur just by chance). It is therefore the differential burdens of proof applied to positive or negative studies that are the crux of the matter here. The authors offer many examples of such instances in their results but I am assuming that beyond the categorisation described, these examples were derived from text analysis. It is difficult to gauge how systematic this text analysis was.

If I have correctly understood the categorisation criteria, the binary characterisations are comparing the authors' conclusion to the ANS panel's own interpretation of results. Assessments
of the potential systematic biases (the balance of false positive vs false negatives) of a diagnostic criteria (here, the ANS panel evaluation) such as those used in medical diagnosis or radar technology in the military are referred to receiver-operating characteristics and require a 'gold standard' of truth to compare the assessment to. Proposing the authors' assessment of their own work as the comparator for ANS evaluation is suggestive of potential bias but does not will not be as convincing as using . In recent years, there have been considerable efforts to develop critical appraisal methods adapted to animal experiments for the purpose of systematic review. I would direct you towards the work of SYRCLE (https://doi.org/10.1186/1471-2288-14-43) or CAMARADES (http://www.dcn.ed.ac.uk/camarades/) for examples of risk-of-bias tools.

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