Reviewer's report

Title: Pharmacokinetic and physiological effects of oral DMAA administration

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Reviewer: Paulo Paixão

Reviewer's report:

The authors presented a pharmacokinetic-pharmacodinamic study on DMAA (Methylhexanamine) after an oral single administration of a capsule with 25 mg on healthy human subjects. The study is, in general, well conducted and allow the PK characterization of this molecule under the tested conditions. This is a company funded study and it is clear that the context behind it are the recent reports on the safety use of this dietary supplement. After the review of the document, the following questions were identified:

- Major Compulsory Revisions

1 - In the background section, it is important to contextualize the current legal status of DMAA that is on ban in various countries, namely Canada, New Zealand, Sweden, Australia, Brazil, UK to name a few. FDA itself had challenged the marketing of DMAA products for lack of safety evidence.

2 - Still in the background section, authors have commented that “several prospective investigations to date using recommended label dose have not shown any side effect”. It is important to further characterize the “recommended” label doses. Looking at one of the products that the authors describe on their paper, Oxyelite pro, there is no indication on the amount of DMAA present on the capsules and the suggested use propose 1-2 capsules on an empty stomach and an additional capsule six to eight hours later. It would be important to compare the expected daily amount of DMAA on these “suggested uses” against the dose presented in the current paper.

3 - The plasma analysis section should be further explained. No references are made to any published study and, as such, indications on the plasma precipitation procedure, columns, eluents, etc. should be presented. The lower limit of quantification of 1-2 ppb is outside the linearity spiked samples (5-50 ppb), and this should be explained. A chromatogram should also be presented.

4 - On the Results section, it is indicated that extremely high blood levels of DMAA were observed in a subject, including a high baseline value. These unexplained results should be presented. What was the baseline value? What was the Cmax on this subject? Was the terminal half-life comparable to the remaining subjects? What was the change on the pharmacodynamic variables on this subject?

5 - On the discussion section, the authors should comment on an interesting paper of Venhuis and Dries (Venhuis, Bastiaan J.; De Kaste, Dries "Scientific
opinion on the regulatory status of 1,3-Dimethylamylamine (DMAA)” European Journal for Food Research and Review 2012 2 (4): 93–100 (http://www.sciencedomain.org/issue.php?id=155&id=1/)). In that paper, the authors concluded that oral DMAA acts as a bronchodilator (above 4 mg), increases heart rate (above 50–75 mg), and increases blood pressure (above 100 mg). They also conclude that serious adverse effects are expected for oral dosages above 200 mg. The studied dose of 25 mg is below these values, but on a multiple dose administration, DMAA plasma concentrations may increase to higher and more relevant levels, and this should be discussed.

6 - Also on the discussion section, the authors reported that the peak plasma DMAA concentrations are 15-30 times lower than those reported on the intoxication case studies and hypothesized that these patients likely ingested dosages of DMAA of 375-750 mg. It is important to mention that these conclusions are based on the assumption of linearity of DMAA PK and on the assumption that no previous DMAA was ingested by the patients. It is also important to mention that no conclusions on linearity can be drawn from the present study, as only one dose strength was tested. It is also important to mention that, assuming this linearity would allow us to simulate plasma profiles on multiple dose administrations and that in this case, a regime of two 50 mg capsules and a 25 mg capsule 6 hours later, a day, would result in plasma DMAA concentrations as high as 230 ng/ml. This value is only 10 times less than the ones reported on the intoxication cases.

- Minor Essential Revisions

7 - There are many bibliography references that are wrongly numbered throughout the document. This should be corrected.

8 - Figure 4 and 5 should be merged, as they contain the same type of information.

- Discretionary Revisions

None

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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