Reviewer's report

Title: Pharmacokinetic and physiological effects of oral DMAA administration

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Reviewer: evelyn lobo

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The authors present the findings on the concentration-time profile of oral DMAA in healthy men following single dose of 25 mg and its effect on vital signs (heart rate, blood pressure and body temperature).

Major comments:

1. The question the authors are addressing is too narrow in scope and therefore limited in its value. The limitations of the current study design is that it does not address the question, what is the pharmacokinetics of oral DMAA on multiple dosing and in the dose range it is marketed as a supplement. An important question to address is what is the maximum tolerated dose of DMAA administration.

2. Background: Lacks sufficient information to understand the relevance and impact of purpose of the study. What is DMAA used for and by who? What is the dose/s it is sold as? An example says 278 mg per capsule. It is unclear what is it used for at high doses or in combination with caffeine/alcohol. What dose range was studied (line 68 to 70)? Lines 92 to 98, didn’t understand how lack of systematic study on safety drives the need to conduct a PK study. Its not clear why heart rate, blood pressure and temperature are being evaluated.

3. Methods: It is unclear what the inclusion and exclusion criteria were for enrolment in the study. Why was DMAA given under fasted condition? Is it how it is directed for use? What is the source of DMAA, marketed source, USP labs?

4. Results: The PK profile of one of the subjects excluded should be showed and concentration values reported. Report the variability in pharmacokinetics as %.

5. Discussion.

Limitations of the work are not clearly stated (see comment 1). Why enrol men only?

Discussion on one individual with higher DMAA concentrations is missing.

Comparison of concentration data in this study to that in the literature needs more discussion. Are they only 2 references that reported concentration values? Difficult to follow the comparison with ref 2,3 (lines 202208. with the concentration reported are not listed. While concentrations are listed for ref 2 in the background, couldn’t find for ref 1. Consider comparing the range of the concentrations in this study to those reported in handful of individuals. Expecting individuals to match with the mean of the population is misleading.

Authors haven’t discussed the scientific reason for why DMAA would be
expected to have an effect on women taking contraceptives or caffeine. There is a pharmacokinetic reason for the drug interaction between caffeine and oral contraceptives.

It is not clear what dose range is safe. What kind of studies have been conducting to investigate the safety or physiologic effects?

Consider stating findings as preliminary, to confirm lack of an effect, one needs placebo controlled randomized study.

6. Conclusion: Lines 270, Higher doses is one potential reason for higher concentrations of DMAA, but there could be others, drug interaction, errors in bioanalytical methods, bioavailability from different sources could vary, variability in exposure, non linear pharmacokinetics etc. Last 2 sentences in the conclusions are irrelevant.

Minor comments:
The order of the title, pharmacokinetic and physiologic effects is not reflected in the order of the results reported.
Line 130: What is biochemistry? Was any lab work done on the subjects? No results reported.
Title should mention that the investigation is in men
Line 76, there appears to be some error, “to consume their condition”? What is Jack3d?
Line 142, consider using ng/mL instead of ppb. Why is lower limit stated as 1 to 2, instead of 1.
Line 190: Use same units minutes vs hr
Line 228: Clarify significance related to statistical vs clinical
Why are the lines not connected between 6 to 24 h for figures 1-3
Can figures 4 and 5 be combined. Showing mean (no SD) and individual profiles.

Level of interest: An article of limited interest

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.