Author's response to reviews

Title: Lack of efficacy of blueberry in nutritional prevention of azoxymethane-initiated cancers of rat small intestine and colon

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Author's response to reviews: see over
Dear Editor and Reviewers:

Thank you for the careful and thoughtful critiques of our manuscript. We have revised the manuscript in accordance with the reviewer’s comments and suggestions, exactly as described below.

Reviewer 1 (Dr. Corpet) -

We appreciate your positive comments on the MS.

1) The additional suggested citation has been added to the text (in Background and Discussion).

2) We have modified the discussion regarding the differences with the Boateng et al study to better emphasize the experimental differences between the two studies and to not simply assign such study differences to blueberry dose (now seems to be an unlikely cause).

Reviewer 2 (Dr. Vinitketkumnuen) -

1) Information regarding anthocyanin content of blueberry is included. We have added text describing why female rats weighed less than males. Although diet consumption was not measured in this experiment, in similar studies in rats fed the purified AIN-93G diet, daily consumption was 23-25 g/day, which would translate into a total anthocyanin intake from blueberry of ~76 mg per day. Based upon energy intake, this would be 0.7 mg anthocyanin per kcal of energy intake. This is a relatively high dose, if translated into a comparable human dose (~1400 mg anthocyanin per day). Because of the very low apparent absorption of anthocyanins and its rapid metabolism, we chose in our initial study to provide a higher dose in order to possibly not miss a biological response.

2) We have added the requested statements regarding criteria for classifying adenomatous polyps and adenocarcinomas.

3) The section in the Discussion regarding apoptosis is from published studies by other laboratories, not our own. Therefore, we have revised the relevant sentence structure so as to not convey this incorrect impression.

4) Regarding C-peptide levels in males and females - we have added the suggested revision.

Reviewer 3 (Dr. Magnuson) –

Thank you for your positive comments on the paper.

1) Regarding C-peptide: we have revised the background statements regarding relevance of C-peptide as suggested.

2) Background statement has been clarified as suggested.

3) In Methods - the rationale for lifetime feeding paradigm was added as suggested.

4) Methods regarding dams - clarified as requested.

5) Methods regarding offspring and AOM - clarified as requested.

6) Regarding animal numbers – we have added text in methods to explain why there were fewer numbers of rats than expected from numbers of dams; this mainly stems from random allocation of some progeny to unrelated studies not described here. Our apologies for this oversight.

7) Tumor number for tissues other than small intestine and colon are now added to Table 4 legend as requested.
8) The requested statement is now added.

9) Requested statement of clarification was made.

10) This is a good point; we have revised the text to indicate that a greater dose of BB should in fact be more protective.

11) Regarding gender differences - we have exhaustively re-searched the literature and used this new information to refine the Discussion regarding the observed gender differences and novelty of results.

12) See response for # 11.

13) Abbreviations are now defined at first use as suggested.

14) Tables 3 and 4 headings are now changed as suggested.

15) Table 3; the requested information was added.

16) Discretionary revisions – we have added the requested number of animals with each tumor to Table 4 and to Figure 3.

On behalf of the co-authors, thanks to all of you for the above comments, which have helped us to strengthen the manuscript. We hope that the paper is now suitable for publication.

Sincerely,

Frank A. Simmen, Ph.D.

Professor