Author's response to reviews

Title: Exposure to Nitro Musks in the Environment and the Characterization of Potential Effects in Animal and Human Cell-line Models: A Review

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Author's response to reviews: see over
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Dear Editor,

On behalf of my coauthors I would like to submit our revised manuscript. We would like to thank the reviewers for their helpful and thorough comments. We have made a number of changes to the paper--here is a summary of the reviewer comments (shown alongside black bullet points) and our changes and responses (open circle bullet points):

Reviewer #1:

- The reviewer pointed out that the title was not representative of the content presented.
  - We have taken their suggestion and changed the title of our manuscript to: Human Exposure to Nitro Musks and the Evaluation of their Potential Toxicity: An Overview

- The reviewer suggested that the organization of the manuscript needed to be revised in order to have a more clear and cohesive manuscript. In particular, they were concerned with the lengthy introduction and the order of the various sections in the discussion.
  - We have reworked this manuscript into 3 sections: an introduction section, a background section and a conclusion section. This is consistent with other review articles in your journal. The introduction section has been shortened to only give a quick overview of the nitro musk chemicals. The background section has been reordered and divided into 4 main areas: Musks in the Environment, Human Exposures, Toxicity and Health Outcomes.

- The reviewer suggested that we include a table that summarizes all of the toxicity data.
  - This table has been created and is titled Appendix 1 and has been included as an addition file.

- The reviewer pointed out that the toxicity data lacked the doses tested as well as the magnitude of the effect.
  - The manuscript has been revised to include this data. Revisions can be seen on pages 9-13 in all paragraphs.

- The reviewer questioned what the SOS in SOS chromotest was referencing.
  - For clarification purposes this has been changed to the equivalent procedural title: E. coli genotoxicity assay.

- The reviewer suggested including an additional study by Lu et. al 2011 on nitromusk concentrations in personal care products.
  - This study has been added under the human exposures section on page 7, paragraph 1.
The reviewer suggested including an additional study by Lu et. al 2011 on measured nitro musks in indoor dust in order to present another route of exposure from an environmental source of nitro musks.

- This study has been included on page 7, paragraph 1.

Reviewer #2

- The reviewer was also concerned about the organization and focus of the paper. This lack of focus led them to question the objective of this paper.
  - As mentioned in our response to reviewer #1 we have reorganized the paper in order to create a more clear and cohesive manuscript. In response to the objective of the review, we have added an additional line at the end of the introduction (page 2 paragraph 1) stating the goal of the review.

- The reviewer was also concerned about that the title was not representative of the content presented.
  - We have changed the title of our manuscript to: Human Exposure to Nitro Musks and the Evaluation of their Potential Toxicity: An Overview

- The reviewer felt that readers would benefit from a discussion of the collected papers given a discrepancy between 2 studies that showed both the inhibition and induction of Cytochrome P450.
  - In order to supplement all of the papers presented, we decided to create a table (appendix 1) based on comments by reviewer #1 that should help present the different studies. In regards to the discrepancy between the Stuard et. al study (1997) and the Schnell et. al study (2009), in the Stuard et al study the authors look at the individual effect of each nitro musk while in the Schnell et. al study is focused on the interactive effect between different musk compositions. This is addressed on page 13, paragraph 1.

- The reviewer’s minor points of including BMI in the abbreviations list and changing ‘then’ to ‘than’ in what is now pg 17 and line 10 has been changed.

Reviewer #3

- In comment #1, the reviewer was concerned that we had chosen to focus on nitro musks while not looking at the effects of polycyclic musks.
  - We chose to focus on nitro musks because we were concerned about their continued use in the United States and other parts of the world even after the ban of their use through REACH in the European Union. It is true that there has been a reduction in the production of nitro musks but there is concern that their remains the potential for exposure not only through household products but through environmental sources such as dust, water and contaminated food because of their persistence in the environment. We have added in an additional source on page 7, paragraph 1 to discuss concentrations of nitro musks found in specific products. We have also added in an additional source discussing potential inhalation exposure to nitro musk through dust in the home on page 7, paragraph 2 in order to argue that there remains additional environmental exposures.
• In comment #2, the reviewer was concerned that the manuscript was not a critical review of the health implication of nitro musks. The reviewer also stated that the manuscript did not include concentrations of exposure levels for the environmental exposures or the exposure concentrations for the animal and human studies.
  o Given the lack of human studies this paper was written to argue for further epidemiologic research for nitro musk exposures. We understand the reviewer’s concerns and feel we have addressed them by reorganizing the paper which we believe better facilitates our argument. We have also added in the exposure levels when available throughout the human exposure section and the toxicity section. The human exposure section discusses levels found in environmental sources. However, because nitro musk exposure through personal care products is widely varied by personal habits and product preferences, the data on average human exposure to nitro musks is lacking. We have however, provided concentrations of nitro musks found in breast milk and fat samples on page 7, paragraph 2 which is more relevant for human health studies since it represents absorbed doses of nitro musks.

• In comment #3, the reviewer expressed similar concerns as reviewer #2. The reviewer commented on a discrepancy between 2 studies that showed both the inhibition and induction of Cytochrome P450. The reviewer also comments on the lack of consistency in the terminology.
  o We have addressed this in the paper by pointing out that the Stuard et al (1997) study the authors look at the individual effect of each nitro musk while in the Schnell et. al (2001) study is focused on the interactive effects between different musk compositions. This is addressed on page 13, paragraph 1 and 2. We have also standardized the terminology which can be seen on page 13, paragraph 1 on line 6 and page 13, paragraph 2, line 8.

Thank you for considering this manuscript.

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