Reviewer's report

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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Reviewer: Kristin Schirmer

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This manuscript overall aims to review available knowledge about environmental exposure and potential health effects elicited by synthetic nitro musks. Synthetic nitro musks, together with polycyclic musks, present a group of chemicals used as fragrances in a wide range of consumer products from parfumes to detergents and cosmetics. Because of their stability (and thus accumulation in the environment) and their potential long-term health effects (especially potential carcinogenicity of nitro musks), their use has long been questions and criticized but continues to be high mainly also because common regulatory tests imply low toxicity. Thus, a critical review on this topic could certainly be useful. The manuscript presented here, however, does not fulfill this goal. It presents an (easy to read) essay that simply collects some available information but does not investigate this information critically or manages to put it into a larger context. As a result, the reader is left with very little to learn, barely touching the surface of the issue. Below I highlight only a few key points that have been completely neglected or presented in non-critical way to potentially help improve this work.

1. As stated above, both nitro musks and polycyclic musks are important fragrances. Musk xylenes are the most common nitro musks (a fact not detailed in the paper). However, especially the nitro musks have been of human health concern for decades because of their potential long-term effects (carcinogenicity) and for this reason have been discontinued in several countries (e.g., Japan, Germany) or products (such as lipstick in the US). Unfortunately, the review misses to reflect on these developments. The authors themselves state that “nitro musks have been largely replaced by polycyclic musks” but then ignore the group of polycyclic musks. I find this decision hard to justify; a review on this topic should certainly include both groups of synthetic musk compounds.

2. For a critical review of the use and potential health implications of these compounds, one needs to reflect on their physico-chemical properties (which could teach you, e.g., why they are only partly attenuated in waste water treatment plants and how animals and humans are exposed), production volumes and measured concentrations both in the environment (air, surface, ground- and drinking water) and as contaminants in food (claimed by the authors to be a major uptake route in humans), and on values of human daily exposure. In fact, throughout the manuscript, a well explored link between measured exposure concentrations and health effect reported in animal or human studies is missing. To provide one example, one sentence on page 6 reads: “Exposure of
pregnant rats to concentrations of musk ketone and musk xylene well above human exposure was not shown to have any adverse effects on the embryo…” – so what is the human exposure? The text goes on: “Eggs that were exposed to musk ketone in the surrounding water had a decreased early life stage survival…” – so what was the exposure concentration in water and how does this relate, e.g. to aqueous concentrations measured in the environment? Finally, it is not sufficient to say “conflicting results were found”, as stated, e.g. at the end of page 7. What actually are the conflicts found in the results? I did not learn this from the manuscript.

3. I am not sure that the author understood all the implications from what they wrote. For example, on page 8 it is stated that musk ketone together with benzo(a)pyrene (BaP) leads to enhanced genotoxicity compared to BaP alone. It is stated that musk ketones apparently induce P4501A and P4501B2 – to me this means that musk ketones likely lead to a faster and possibly stronger transformation of BaP to BaP epoxides, which are known to be genotoxic. That P450, especially P4501A is the phase I biotransformation enzyme to lead to BaP epoxide formation has long been known. Instead of making this link, the authors write that P4501A and P4501B2 cause hepatocellular hypertrophy… I have never heard that biotransformation enzymes per se can do this. To make these statements even more confusing, the authors state on page 9 that musk ketones have been shown to inhibit CYP1A in carp. Now CYP1A is the new terminology for P4501A. This means that, if citations are correct, musk ketones have been implied to induce or inhibit P4501A. The authors do not make this link or try to explain the basis for these seemingly opposite results, leaving the reader puzzled.

**Level of interest:** Too insignificant to warrant publication in any journal

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

There are not competing interests considering the questions above.