Reviewers' answer to authors' responses to the second review round for AOP 263.

July 22, 2021.

Dear Authors, Dr. Song and Dr. Villeneuve,

Dear Editor Knapen,

We appreciate the authors' consideration and detailed responses to the remaining comments we've provided in the second review round. We are pleased to inform that we support the way forward proposed by the authors (see also our specific answers to some of the authors' responses below). Hence, we recommend that, after appropriate changes to the manuscript and the AOP-wiki have been made, the manuscript be accepted for publication in ET&C. We thank the editor and the authors for organizing and carrying through this collaborative review process, which provided a valuable learning experience for us as well.

Sincerely,

Ksenia Groh
David Dreier
Joel Meyer
Terry Schultz

Answer to response #1: We appreciate the detailed discussion provided by the authors in response to our remaining request to consider splitting the MIE "coupling of OXPHOS, decrease" into two separate KEs. We understand the authors' position and arguments against the complete splitting, particularly related to the lack of experimental approaches to directly measure the uncoupling action by methods other than dissipation of PMF. Consequently, we support the authors' suggestion to implement the "Event Components" approach and "keep the lumped MIE term of 'decreased coupling of OXPHOS', but differentiating 'diffusion across the IMM and transport protons out (uncoupling action)' and 'dissipation of PMF' as two event components associated with this MIE." This solution appears to fully address the anticipated needs, as it provides the possibility to connect to other AOPs and/or upgrade to separate KEs in the future, and at the same time allows keeping the originally developed AOP structure and making the best use of the evidence already collected by the authors.

Answer to response #3: We thank the authors for the detailed discussion of this point as well and concede to their decision to not include partitioning of the stressor as an initiating event.

Answer to response #4: We thank the authors for the provided explanations and suggest to adhere to "alternative solution" they've proposed, namely to "add a few more sentences in the report to state that population decline is a potential higher level AO linked to growth inhibition, but the relationship warrants further development for empirical support."