To the Editor,

We would like to thank Anderson and Michaelis, the authors of the Letter to the Editor, for their comments assessing our work, however, many points that they have raised demonstrate a lack of understanding of the systematic review process. There are also several instances within the letter which demonstrate a misrepresentation of our work, and several unjustified claims made to seemingly support arguments without requiring the rigor of publication review. We address several of these with the following rebuttal.

Throughout their letter, Anderson and Michaelis express concern as to how individual resources were selected and how this review could be considered systematic or the most comprehensive to date. We would like to direct the authors to the PRISMA Guidelines 2009 statement for systematic reviews and meta-analyses (Moher et al., 2009). As described within the methods section of the manuscript, all relevant portions of these guidelines were followed or exceeded in the construction of the review. The complete search terms are provided to the reader within the manuscript, and should the authors wish to replicate the study, they will recover the same resources from the search with publication dates up to January 15th, 2021, for the databases chosen. Of the total 138 resources reviewed in the study, 116 were dictated by the selection criteria of the systematic review. Additional supplementation of 22 papers that did not appear as a result of the systematic review searches were included. These articles are identified and justified within the supplementary information. This transparent and unbiased resource selection is what makes this review systematic and more robust than selecting papers based on our “familiarity with the literature” which appears to be the approach suggested by Anderson and Michaelis.

When discussing the scope of the manuscript, the authors of the letter felt that it was "fractured and overly broad." We agree that we cast a wide net when approaching this subject and did so intentionally as this represents what is in the literature in an unbiased way. We feel that it is vital to examine potential confounding variables such as ozone, pesticides, and humidity on aircraft that may be partly or wholly responsible for some of the symptomology described by flight attendants and pilots. The inclusion of these factors more explicitly describes the actual conditions for workers, much more so than simply focusing on oil fumes as suggested by the authors. We understand the topic of occupational exposure on aircraft to be highly contentious and hotly debated, the findings recorded by research funded by advocacy groups often differ from research funded by industry. Our research was completely independent and aims to comprehensively include papers from all positions so that the readers can have access to a representative sample of the available literature. It would not be correct for us to only focus on specific papers that align with our own personal beliefs. Instead we encourage readers to investigate the literature for themselves and come to their own conclusions.

Advocacy, as opposed to science, is likely a significant factor for Anderson and Michaelis’ writing their letter to the editor. Anderson and Michaelis appear to be using this platform to restate and emphasize information available within the review when it serves their purpose. Some direct quotes from the two manuscripts that illustrate this point are as follows:

Anderson and Michaelis - "the cited exposure limits were not developed for application in an enclosed, reduced-pressure, workspace that transports members of the public (i.e., not workers) and requires the workers who are present to be particularly alert to fly the aircraft and manage security in the cabin."

Hayes et al. - "*In support of this claim are several studies: Wolkoff et al. (2015), Schuchardt et al. (2019), and de Ree et al. (2015); that suggest there is a limited, if any, chemical contribution occupational risk for aircrew. This is based mainly upon threshold values established for industrial work. Some of the manuscript results are described as conclusive or not meeting the definition of occupationally related disease in the study's respective country. However, the prescribed threshold limits cited in these studies are not explicitly designed for, and may not be adequately suited to, the aircraft environment. Watterson and Michaelis (2017) discuss some of the established threshold limits' failings: They do not consider differences in sensitivities or sensitization of workers, atmospheric pressures, and time of exposure. Additionally, the authors state that threshold limit values (TLVs) are for individual compounds and are not suited for complex mixtures. Multiple sources within the Watterson and Michaelis (2017) manuscript are quoted as stating that TLVs or occupational exposure standards are not well suited to the aircraft environment, including the Aerospace Medical Association, ASHRAE, EASA, aircraft manufacturers, and other industry sources.*"

Anderson and Michaelis - "the majority of sampling data collected on aircraft only represent a very small subset of the chemical compounds identified in oil fumes, for example, (Michaelis, 2007 and SHK, 2001) and in cabin air generally (Guan et al., 2014). The toxicity of a small subset of individual constituents is not equivalent to the toxicity of the mixture."

Hayes et al- "*The concentrations of compounds of concern on aircraft are described within most reviewed manuscripts as low; however, the full exposome onboard aircraft is undescribed. The bulk of manuscripts have focused on certain organophosphates and VOCs, often due to the availability of suitable standards (SI-Table 2). However, these substances make up only a portion of what one is potentially exposed to onboard the aircraft (Winder and Balouet, 2002).*"
Hayes et al.- "*However, the sampling of aircraft has not yet identified a contaminant or mixture of contaminants in sufficient concentration proven to be capable of the symptomology. Further research is required to determine this contaminant or mixture should it exist, and further evidence of the impacts of chronic low dose exposure and susceptibility studies are required for the known contaminants*."
Hayes et al.- "*There is little question that individuals are ill, and there is strong evidence that it is related occupational exposure but no one class of, or specified contaminant, has been demonstrably harmful; it seems likely that the unknown multiplicative or synergistic effects of the exposure mixture and the cumulative effects of extended exposure, are resulting in the described illness.*"

We would also like to address the concerns raised about supposed unsuitable references and invalid claims. Anderson and Michaelis's description of why the Occupational Safety and Health act information was included is misinterpreted. Immediately following the description of the act in the paper, we address that "[i]t is evident that occupational hazards are associated with flight for pilots and flight attendants." Additionally, it is our understanding that in the USA, while the FAA has jurisdiction over the occupational safety of flight deck crew while the aircraft is in operation, flight attendants and other aviation workers fall under OSHA purview; this is detailed in a memorandum of understanding between the two agencies (FAA, 2000).

The authors also describe the use of Bagshaw and Illig's "The Aircraft Cabin Environment" assumedly 2019, as no 2016 article is cited for these authors, as being an unsuitable reference resulting in an invalid claim. Anderson and Michaelis state that there are two sentences of importance related to chemical contamination (oil fumes) in the cabin. Here are those two sentences: "Concerns have been expressed that oil fumes may be present in cabin air as a result of leakage into the engine bleed air. Independent research has so far failed to confirm adverse health effects caused by such minor and intermittent cabin air contamination" (Bagshaw and Illig, 2019). They claim that the use of this assessment is invalid due to the citation of two irrelevant sources; the sources in question include the Crump et al., 2011 Cranfield study in which 100 flights were explicitly sampled for cabin air contaminants, including oil fumes. The other source Bagshaw and Illig cited was a book, "The Airliner Cabin Environment and the Health of Passengers and Crew," National Academies of Sciences, Engineering, and Medicine (2002), and the claims of Anderson and Michaelis that this book only describes biological contamination are false. Provided are direct quotes from Chapter 2 - Environmental Control - 1) "However, other contaminants can be in the outside air, such as ozone (O_3) or can be picked up in the air supply system, such as leaking oil "; 2) "If the air is compressed just enough to pressurize the cabin rather than being compressed to a point where it can operate rotating air-cycle equipment, the temperatures attained in the compression could possibly be limited enough to avoid pyrolysis of contaminants, such as hydraulic fluid or lubricating oils " (NRC, 2002). The cited sources are clearly valid.

Furthermore, immediately following the supposed unsuitable/invalid claim in our manuscript, we provide additional sources that support the claim beyond Bagshaw and Illig. Here are the sentences in question from our manuscript:

"*Concern has been raised that research has not adequately confirmed that health impacts result from chemical contamination of the aircraft cabin, primarily based upon the intermittency and lack of severity of exposure (Bagshaw and Illig, 2019). In support of this claim are several studies: Wolkoff et al. (2015), Schuchardt et al. (2019), and de Ree et al. (2015); that suggest there is a limited, if any, chemical contribution occupational risk for aircrew*".

We wish to be clear, this is not our opinion; it is representative of what was reported by those authors in the literature. If Anderson and Michaelis have any concerns with the scientific validity of those studies then their comments are better focused towards those manuscripts rather than this systematic review which is designed to review the literature that is available. To describe our usage of the quote attached to this citation as an unsuitable reference is disingenuous and appears to be an attempt to dismiss portions of an argument that Anderson and Michaelis do not agree with.

Finally, we ask readers of these letters to the editor to examine the second paragraph in section 4 of our manuscript. This should provide insight into why portions of our manuscript were inappropriately disparaged.

Hayes et al.- "*It is evident within the literature that there are opposing viewpoints in determining occupational exposure risk to flight crew. Of the experimental manuscripts reviewed, 38% made declarative statements in favor of, or opposed to, the occupational risk of chemical exposure within the cabin and 62% did not. Within the declarative subset, those papers which were determined to be in favor of occupational risk acknowledged stakeholders in 33% of the manuscripts. Those manuscripts which were opposed to occupational risk acknowledged stakeholders in 67% of the cases. Stakeholders included pilot and flight attendant unions, advocacy groups, aircraft manufacturers, and operation firms. When pilot and flight attendant unions or advocacy groups were acknowledged, 80% found in favor of occupational risk, none were opposed, and the remaining 20% undeclared. When airline manufactures and operator stakeholders were acknowledged, 5% were in favor of occupational risk, 42% were opposed, and 53% were undeclared.*"

We thank the Editor for the opportunity to provide a rebuttal.

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