

Global warming risks dehydrating and inflaming human airways

Corresponding Author: Professor David Edwards

This file contains all editorial decision letters in order by version, followed by all author rebuttals in order by version.

Version 0:

Decision Letter:

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Dear Professor Edwards,

Please allow me to apologise for the delay in sending a decision on your manuscript titled "Global warming is dehydrating and inflaming human airways". It has now been seen by 2 reviewers, whose comments are appended below. You will see that they find your work of some potential interest. However, they have raised quite substantial concerns that must be addressed. In light of these comments, we cannot accept the manuscript for publication, but would be interested in considering a revised version that fully addresses these serious concerns.

We hope you will find the reviewers' comments useful as you decide how to proceed. In addition, for publication in Communications Earth & Environment to be appropriate, we will need you to

- * provide compelling new insights into the impacts of dehydration stresses as a result climate warming on human airways,
- * discuss hydration process in the human airways more comprehensively, including clear and complete definitions of all terms, and
- * ensure the level of confidence in your language (especially in title and abstract) adequately reflects the caveats and uncertainties.

Should additional work allow you to address these criticisms, we would be happy to look at a substantially revised manuscript. If you choose to take up this option, please either highlight all changes in the manuscript text file, or provide a list of the changes to the manuscript with your responses to the reviewers.

When resubmitting, please provide a point-by-point response to the reviewers' comments. Please submit your responses as a separate file, distinct from your cover letter where you can add responses to the Editors' comments that you do not want to be made available to the reviewers. Word files are preferred. We recommend that any figures, tables or graphs that are included in the response to reviewers are also included in the main article or Supplementary Information.

Please bear in mind that we will be reluctant to approach the reviewers again in the absence of substantial revisions.

If the revision process takes significantly longer than three months, we will be happy to reconsider your paper at a later date, as long as nothing similar has been accepted for publication at Communications Earth & Environment or published elsewhere in the meantime.

We are committed to providing a fair and constructive peer-review process. Please do not hesitate to contact us if you wish to discuss the revision in more detail.

Please use the following link to submit your revised manuscript, point-by-point response to the reviewers' comments with a list of your changes to the manuscript text (which should be in a separate document to any cover letter), a tracked-changes version of the manuscript (as a PDF file) and any completed checklist:

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Please do not hesitate to contact us if you have any questions or would like to discuss the required revisions further. Thank you for the opportunity to review your work.

Best regards,

Heike Langenberg, PhD
Chief Editor
Communications Earth & Environment

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REVIEWER COMMENTS:

Reviewer #1 (Remarks to the Author):

The authors examined how hot, cold, and dry air compresses the airway epithelia and increases the secretion of inflammatory cytokines. In this manuscript, the authors presented interesting topic. However, there are some suggestions to improve the paper:

1. Please clarify the institution associated with Boston University, as referenced in citations 4 and 5.
2. It would be helpful if the authors provided a clearer background, specifically explaining what dehydration stress entails and how global warming poses a threat to human airways
3. Is there any reference provided for the climate change model used by the authors in this study?
4. Line 54: The phrase 'We report the results of our studies here' could be improved by removing it.
5. It would also be better if the authors clearly stated the definitions of hot, cold, and dry air.
6. It would be better if the authors clearly stated the objective of this study in the manuscript.
7. It would improve readability if the authors shortened the section on upper airway mucus exhibiting transpiration behavior and included it in the Supplementary Materials.
8. Some abbreviations are not clearly defined in the manuscript. It would be better if the authors clarified them.
9. Lines 208-210: It would be better if the authors mentioned 'Table 2' only once.
10. It would be preferable if the authors clearly separated the sections in the results for hot, cold, and dry air.
11. It would be better if the authors clearly separated the chapters for the Introduction, Methods, Results, and Discussion to enhance clarity.
12. Lines 246-250: It would be better if the authors refrained from repeating the results in the Discussion section by referencing tables and figures. They should focus on highlighting the novelty and important findings of this study.
13. It would be better if the authors mentioned the limitations of this study.

Reviewer #2 (Remarks to the Author):

Comments on the article "Global warming is dehydrating and inflaming human airways".

In this article, the authors develop an interesting and comprehensive model of the evapotranspiration dynamics occurring in the airways, especially in the upper part of the respiratory system. This mathematical model and the associated numerical simulations are then compared with in vitro measurements of the fluid exchange dynamics of the ASL of human epithelial

cells cultures. Finally, these results are used to extrapolate the behavior and dynamics of the human respiratory system to global warming in the US in the present time and late 21st century.

This interesting and comprehensive article sums up a strong corpus of insights and knowledge in the transport and exchange dynamics in the human respiratory system, and contributes definitely to a better understanding of this complex and intricate dynamics.

However, its reading rises numerous questions and comments that I would like to write in this report. I will try to progress from general to minor comments, as well as possible.

1. VPD: the concept of water vapor pressure deficit (or VPD) is at the core of this article, in the modelling as well as in the results and extrapolating part of it. In my opinion, this concept is not trivial at all, and is connected to branches of physical chemistry and thermodynamics that are not easy at all to understand and master. Thus, I have been surprised that this core concept has not been defined more properly, barely in few sentences. As an example, the definition is appended by Fig 1A in which the different pressures are not properly defined neither. I would definitely suggest that the authors amend the manuscript to outline and define more properly this major concept.

2. Mucus hydration, dehydration and water replenishment: it is known and has been highlighted, namely through the work of Widdicombe and colleagues for example, that the epithelial cells are constantly replenished in water their water content through interactions with the surrounding tissues. This is evoked by the present authors, but not properly referenced. In addition, modelling approaches (Karamaoun, Tawhai, for example) have confirmed and explored this dynamics. It appears that, in equilibrium conditions, the average water replenishment flux interestingly matches the evaporation losses through the ventilation cycle. Regarding these losses, the authors write that major aspect of breathing: even in standard conditions, the human respiratory tract is a site of water losses. But why? This is not mentioned nor explained by the authors, to the best of my knowledge. In my opinion, this is a tricky and major aspect of the steady-state hypothesis of the volume conservation of the ASL: over a respiratory cycle, the evaporation during inspiration is not compensated by condensation during expiration. This water deficit is compensated by water replenishment, in essence, although it is not totally true (see below). I would suggest that the authors mention this point explicitly. I will explain why it is concerning in the next point.

3. Mucus displacement: linked with my previous comment, it has been demonstrated that the displacement of the mucus layer along the respiratory tract is linked profoundly with the hydration status of the ASL (Karamaoun, Tawhai, namely). Without this dynamics, the replenishment would not be sufficient to compensate the evaporation in the upper respiratory tract, and there would be mucus accumulation in the distal part of the airways on the other hand. The authors should evaluate the pertinence of this point in line with their modelling approach. In my opinion, it is not even true to make the hypothesis (see Fig 1D) that there is an equilibrium between evaporation and replenishment in steady-state, without including mucus displacement. Please comment and/or correct, and add references for the epithelial replenishment flux values.

4. Airways conditioning: I would be more convinced by the results and the conclusions of the authors if the question of air conditioning in the respiratory tract would be analyzed more thoroughly. Indeed, many authors (Haut, Bougault, Noël & Mauroy, and plenty of others) have studied and discussed this major aspect of the water balance in the airways, in human and even in the whole mammalian class. Briefly, the air conditioning is a vital aspect of this balance: without conditioning, the water balance would not be maintained at all in the airways, especially in the bronchial part. This conditioning, even in harsh atmospheric conditions, ensures that the temperatures and RH of the airways (from the trachea and lower, at least, but it is always true for higher parts of the tract during nose breathing) are maintained in a range that is compatible without tissue viability, reducing (but not always preventing) epithelial damage (Dempsey, Bougault, Blain, Karamaoun, etc.). Even in drastic conditions, the temperatures and RH in the lungs are maintained to levels that are compatible with cell viability (McFadden, Dempsey, Bougault for experimental conditions, namely; Karamaoun, Haut, Tawhai, Mauroy for numerical simulations, namely). Thus, to be honest, I need to be more convinced by the strong conclusions of this article, especially when such ranges of T and RH are considered. In my opinion, except in the very proximal parts of the tract (nostrils and central nose, mouth and slightly deeper), the range presented seems to be too wide. It is true that the authors briefly discuss the mouth breathing habits at the end of the article; however, I still consider that this point is underestimated and, in my opinion, could impact and reduce the message and conclusions of this work.

5. Title and conclusion: regarding the conclusions, and thus the title in itself, I am not convinced that the results, at this stage (see points above), allow to extrapolate and conclude in such a strong and disruptive manner. Thus, at this point, I think that the title of the article is not appropriate and overconfident. This study, which from a modelling and experimental points of view is very impressive and brings many insights to our research field, does not lead at this stage to such strong conclusions and assertive title. I would appreciate that, in light with my previous points and this one, my (relatively strong) point of view would be discussed and commented. This is a major concern for me.

6. Discussion: in my humble opinion, probably with a bias due to my sound interest in this field of research, I have been disappointed by the discussion and conclusion parts. Many aspects are barely discussed and commented, and a large part of this section, entitled "Discussion", is actually made of conclusive remarks and perspectives. I would appreciate if the discussion aspects (see points above) would be more exhaustive, adding confidence in the results of the present study, which are not negligible at all.

7. General remark for the figures: the resolution and quality of the figures are too low. These figures are at the center of the results presented here, and should be more clear and impacting. This should be corrected.

8. References: the references list, in the text and especially in the Annex, is not clear at all and not homogenized. DOIs sometimes present, sometimes not. Links to article instead of proper citations, formatting issues, ... For me, although I know this part of the literature pretty well, going through the references had been really complicated. Please improve this section.

I will not go further in my comments at this stage. I have been thrilled to read this impressive article, especially from the modelling point of view. I have more comments regarding the modelling part but I do not want to make my report too heavy and come back to these aspects later.

Best regards.

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Version 1:

Decision Letter:

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Dear Professor Edwards,

Your manuscript titled "Global warming risks dehydrating and inflaming human airways" has now been seen by our reviewers, whose comments appear below. In light of their advice we are delighted to say that we are happy, in principle, to publish a suitably revised version in Communications Earth & Environment.

We therefore invite you to revise your paper one last time to address the remaining concerns of our reviewers. At the same time we ask that you edit your manuscript to comply with our format requirements and to maximise the accessibility and therefore the impact of your work.

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Best regards,

Alienor Lavergne, PhD
Senior Editor
ORCID: 0000-0002-4591-1217
Communications Earth & Environment

REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

This is a revised manuscript. Most of the comments have been addressed adequately in the current version.

Reviewer #2 (Remarks to the Author):

Dear authors,

I would like to acknowledge the tremendous amount of work performed in order to produce this revised version.

I estimate that the authors have answered strongly to the comments of the reviewers. The revised version is more solid, compact and structured. The figures are clear ; the results are adequately presented and commented.

I have no further comments nor corrections to add to this revised version, and am curious and excited about the future reception of this very interesting work by our community.

Best regards.

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The authors wish to thank the reviewers for their many helpful comments. In light of these reviews, we have substantially revised our manuscript. We share below detailed responses to each of the reviewer questions and comments.

Reviewer: 1

We thank the reviewer for many helpful comments and suggestions for manuscript improvement. Our response to each comment is provided below:

1. The BU institutions of two of our coauthors were not distinguished in the author affiliations provided by the original manuscript.

Response: This has been corrected and clarified in the revised manuscript.

2. The reviewer asks for a clearer background including articulation of the meaning of hot, cold and dry atmospheres.

Response: The revised abstract and introduction define these extreme atmospheres as sharing a common feature of high vapor pressure deficit. We state temperature and relative humidity parameters for each atmosphere. In our revised introduction we more clearly establish the link between respiratory dysfunction in extreme atmospheres and high VPD, and the latter with global warming. Our intention is to more clearly frame the objective of the study.

3. The reviewer asks for the reference to the climate model to be stated in the introduction.

Response: We provide this reference in the revised introduction.

4. The reviewer proposes we eliminate an unnecessary sentence at the end of the introduction

Response: The sentence has been removed.

5. The reviewer asks for a clear definition of the cold, hot and dry atmospheres.

Response: We have given this definition in the revised abstract/introduction to the paper.

6. The reviewer asks that we more clearly state the objective of the study.

Response: We have more clearly defined the objective of the study at the end of the revised introduction

7. The reviewer suggests shortening the transpiration section and placing some of this material in the supplemental materials.

Response: In our revision we have removed a significant section of the original transpiration section [including the original Eqs (1) and (2)] and refer the reader to the SM.

8. The reviewer asks that all abbreviations be clearly defined.

Response. We have defined all abbreviations introduced in the revised manuscript.

9. The reviewer asks that we do not repeat reference to Table 2 multiple times in the same paragraph.

Response. We have reduced references to Table 2 in this paragraph to a single reference.

10. The reviewer suggests we divide results in terms of cold, hot and dry air.

Response: We hope the clarity in the introduction, notably that these three atmospheres are identical in their evaporative stress on human upper airways when classified by VPD, helps rationalize the focus, from the start of the Results section, on VPD and the inflammatory risks associated with its magnitude. The revised caption to Table 1 adds further clarification of the cold, hot and dry air origins of high VPD.

11. The reviewer asks for clear Results/Methods delineation of the manuscript.

Response. We have delineated the sections of the revised manuscript as requested.

12. The reviewer asks for clarity on the limitations of our study in the discussion section.

Response. We have introduced a paragraph on limitations in the revised manuscript.

Reviewer: 2

The reviewer raises several important points to be clarified in the manuscript for accuracy and comprehensibility. Our responses to these points, and associated revisions to the manuscript, are provided below.

1. The reviewer asks that the concept of VPD be more clearly explained at the outset of the article and its meaning in light of Figure 1 be clarified.

Response: We have revised our introduction to better explain the meaning of VPD and the reason for its centrality in the exploration of extreme atmospheric impact on respiratory health. We have also revised the caption to Figure 1.

2. The reviewer points out that water is lost from the airways with every breath, notably that less than 100% of water evaporated from the upper airways is condensed on exhalation — and that this water is drawn from surrounding tissues. The reviewer wishes this point to be made explicit and for better referencing of the background literature.

Response: We have expanded our references to theoretical and experimental reports of water movement and airway conditioning of inhaled air in the revised introduction, results and discussion sections. We have also rewritten the caption to Table 1 (where the conditioning of inhaled air is explicitly addressed) and note that only 33% of water evaporated on inhalation is condensed on exhalation. In this context, we refer to an earlier paper (34), where we consider mucus transpiration in the light of overall water balance in the airways.

3. The reviewer questions how our analysis can neglect the issues of mucus displacement that are clearly critical to avoiding mucus accumulation in distal regions of the lungs.

Response: In the introductory paragraph to the results section we now address this issue of mucus displacement. We clarify that mucus movement (from the distal regions of the lungs toward the trachea) does not significantly contribute to the (one-dimensional) evaporative transport description, given the very different time scales involved. Turnover of ASL volume by mucus displacement takes approximately 30 minutes in a highly hydrated trachea (where displacement rate is around 4-5 mm/min), whereas ASL volume turnover by evaporation takes around 2-3 minutes (assuming 0.2 $\mu\text{m/s}$ evaporation rate and 30 μm ASL thickness). We further note in the caption to Table 1 that water movement from the lower airways occurs and also contributes to water capacity for evaporation, while noting (as in point 2 above) that the contribution of water movement from lower airways to the evaporative flux of water from the trachea into the lumen is necessarily very small. That this is so reinforces the many theoretical and (in vitro) experimental studies of airway transport mechanisms that we refer to in the revised manuscript.

4. The reviewer questions whether the dry air (low RH, high VPD) conditions reflected in Table 1, modeled in Figure 2, and experimentally evaluated in Figure 3 are realistic — and asks for greater clarity on the consistency of our data and assumptions with the many publications on the subject of air conditioning in human airways.

Response: We have discussed in greater detail the literature in light of oral versus nasal breathing in the revised manuscript, and notably in the caption to Table 1, where we note our estimates of evaporation rates and VPD are in close agreement with the literature. Nevertheless, we agree with the reviewer that proving air of high VPD does actually enter the upper airways on normal tidal breathing with deliver inflammatory consequence is essential to the overall aim of

our manuscript. To address this question, we therefore did the in vivo experiments in mice that are described in the revised manuscript. Briefly, given our theoretical prediction that dehydrated/diseased airways will respond with greater inflammation (greater cell compression) than hydrated/healthy airways (Fig 2), we studied wild-type and mice genetically-modified (Scnn1b-Tg+) to exhibit dehydrated airways reflective of respiratory disease. As reported in the revised manuscript, exposure twice a day for only 15 minutes each day for 7 days led to inflammatory cell infiltration and consolidation particularly in the genetically modified mice. Intermittent dry air exposure amounting to ~ 1% of each day for a week in normal tidal breathing conditions is inflammatory in the mouse model. We hope these results and the fuller references to the literature will adequately respond to the reviewer's question.

5. The reviewer questions the title of our article.

Response: In response to the reviewer's comment, we have modified the title to underline that our study points to the inflammatory *risks* of global warming to human breathing. To summarize why we believe this appropriate: We have identified VPD exposure on oral breathing as a risk to human respiratory health. Our estimates of exposure risk are based on current literature understanding of upper airway exposure to atmospheric conditions on oral breathing in humans. We have mathematically analyzed mucus transpiration and obtained findings— mucus thinning and compression elevation — that are consistent with results obtained (13) for artificial hydrogels undergoing transpiration. Our in vitro ALI culture studies reveal inflammatory cytokine secretion that is similar in nature to that which has been observed over the last several decades following the direct mechanical compression of airway epithelia. We have studied the impact of intermittent dry air exposure on mice, and observed signatures of inflammation that are consistent with our in vitro data, with our theoretical predictions, and with the pathogenesis of chronic respiratory disease. Finally, we have modeled VPD risk in the continental US with an established climate model, highlighting risks of airway inflammation based on our theoretical and experimental (in vitro and in vivo) findings. We believe therefore to have demonstrated the existence of these risks. These risks are consistent with human respiratory dysfunction and disease aggravation by extreme atmospheric conditions. We hope this modification of our title will be seen by the reviewer as responsive and appropriate to the comments made.

6. The reviewer asks that the discussion be more complete.

Response: We have rewritten our discussion to avoid repetition of findings and hope to have addressed the reviewer's concern.

7. The reviewer points out that the references are not consistent.

Response. We have harmonized the references including in the Methods section and supplemental material.

We thank both reviewers for their comments on our revised manuscript. Specific replies to their latest comments are shared below along with the reviewer comments.

Reviewer #1 (Remarks to the Author):

This is a revised manuscript. Most of the comments have been addressed adequately in the current version.

Author response: We wish to thank the reviewer for many helpful comments in the first review, as well as for acknowledging that most comments have been adequately addressed in the revised manuscript.

Reviewer #2 (Remarks to the Author):

Dear authors,

I would like to acknowledge the tremendous amount of work performed in order to produce this revised version.

I estimate that the authors have answered strongly to the comments of the reviewers. The revised version is more solid, compact and structured. The figures are clear ; the results are adequately presented and commented.

I have no further comments nor corrections to add to this revised version, and am curious and excited about the future reception of this very interesting work by our community.

Best regards.

Author Response: We thank the reviewer for recognizing the effort we made in responding to the reviewer's earlier comments. The reviewer's earlier comments were in fact extremely helpful to us. We are also grateful for the expressions of curiosity and support for the role our work may play in advancing the field.