Headache CO2 Induced CLIFF Peer Review

1. *Strength of evidence presented in CLIFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment?*

   Score: 2

   Grading Scale:

   4 - Confident

   3 - Somewhat confident

   2 – Neutral

   1 – Somewhat unconfident

   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2* *Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC* *Loss of Crew and probability*	*Table 4 - Clinical Phase 1, 2 durations* *Table 5 – CP 2 Loss of Crew*	*Table 4 – RTDC %* *Table 6 – RTDC Loss of Crew*	*Table 4 – Loss of Crew Life %* *Table 7 – Loss of Crew Life, Loss of Crew*	*Table 8 – TI*
Score	*2*	*2*	*2*	*3*	*3*	*3*

Comments and limitations:

1. **General comments.** Levels of CO2 above 2% are known to cause symptoms including dyspnea, diaphoresis, lethargy, headache, and confusion. As the length of exposure and CO2 concentration increases, symptoms can progress to loss of consciousness, convulsions and eventually death from asphyxiation. Maintaining an acceptable level of CO2 in a spacecraft can be a difficult engineering task that requires CO2 removal and proper ventilation. Enclosed spaces may have higher CO2 levels, which can be particularly problematic in sleeping quarters. Excursions in CO2 levels are not uncommon over the course of a day in spaceflight and determining acceptable limits on CO2 concentrations has been challenging. Over the lifetime of ISS, the upper limits on CO2 have been reduced over concerns for headaches. Given that headaches from elevated CO2 levels may be similar in presentation to other cephalgias (tension or migraine headache, for example) determining the precise etiology of headaches (non-CO2 related headaches are the subject of another CLIFF) can be difficult. Finally, the levels of CO2 will be dependent on the spacecraft's environmental system design; thus, prediction of what that might be makes predicting the incidence difficult. CO2 exposure training is an important tool to educate astronauts about their potential acute CO2 symptoms.

Several episodes of potential CO2 headaches have been reported during spaceflight. Usually these are easily reversible by providing increased ventilation.

2. **Incidence.** A model developed by Law, et al. was used to determine the probability of headache at a given CO2 concentration over the course of a week. A CO2 level that is typically encountered on the ISS was compared to the probability of headache from the normal CO2 concentration at sea level. Under the assumption that this relationship remains constant, an incidence distribution was calculated. There are a number of unavoidable limitations. CO2 concentrations do not remain constant on spacecraft and can vary by the hour. There are local pockets of higher CO2 levels. Excursions of CO2 levels above the assumed value can lead to much higher incidences of headache as the relationship between the number of headaches and an increase in CO2 levels is not linear. Most importantly, we are assuming that the ventilation and CO2 removal capability of exploration spacecraft will be similar to ISS which may not be the case. These assumptions were used to develop a gamma distribution to approximate the distribution of the incidence of CO2-related headache. The resulting distribution has a mean of 0.686 per person year and standard deviation of 0.587. The best case/worst case probability was based on subject matter opinion. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. The probability density curve that was derived appears to be a reasonable representation of the data presented.

3. **Clinical phase data**. I am in agreement with the clinical phase 1 duration entered in this CLIFF. This data was compiled by a team of expert clinicians, and I was involved in the discussions leading to the calculation of the clinical phase duration. CP2 duration was supported by terrestrial evidence.

4. **Task impairment**. The analysis was performed and reviewed by a separate team of expert clinicians. I am aware of the methods that were used but did not directly participate in the discussions.

5. **Dependence on mission phase or duration of mission**. This medical condition should not be dependent on mission phase with the exception that during EVA's, the suit has its own self-contained ECLSS system.

6. **Limitations**

- There is sparse terrestrial data to inform CP2 and best case-worst case probability split.
- There were a number of assumptions that needed to be made to derive the composite incidence. These could lead to inaccuracies.
    - CO2 concentrations do not remain constant on spacecraft and can vary by the hour.
    - There are local pockets of higher CO2 levels.
    - Excursions of CO2 levels above the assumed value can lead to much higher incidences of headache as the relationship between the number of headaches and an increase in CO2 levels is not linear.
    - The assumption is that the ventilation and CO2 removal capability of exploration spacecraft will be similar to ISS which may not be the case and may result in higher or lower CO2 concentrations.
- Because of the large sample size, the study used to compute the composite incidence most likely overestimates the confidence we have in the assigned value.
- Under-reporting for this condition could have been significant during past space missions due to subtle disease that may not have been apparent to the crew. This may

have affected the development of the model that was used and result in underestimation of the incidence.

Reviewed by:

David C. Hilmers