Toxic Inhalation Exposure 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*	*3*	*3*	*2*	*3*

Comments and limitations:

1. **General comments.** This CLiFF describes toxic inhalation exposure from an irritant or corrosive material during spaceflight resulting in inflammation and/or chemical pneumonitis in the bronchopulmonary tree. A number of toxic inhalation exposures have happened during the history of manned spaceflight. The nature and severity of a toxic inhalation exposure varies widely and is dependent upon the toxic properties of the individual substance. Predicting the incidence of toxic injuries along with their severity is difficult without knowledge of the exact hazardous substances carried on board. The risk also depends on the engineering safeguards built into the system to mitigate the risk of exposure. This CLiFF excludes inhalation of combustion products and respiratory failure as these conditions are covered in other CLiFFs. Toxic dermal exposure is covered in ICL 109. The best case is considered to be an exposure to an inhaled toxin with symptoms that are mild and self-limited. The worst case is an exposure to an inhaled toxin that requires treatment but does not result in ARDS/Respiratory Failure (covered in another CLiFF).

2. **Incidence.** There have been a number of incidents of inhalation of toxic substances during spaceflight. These are summarized in several reports by James in 1998, 2011, 2019. Each case was

reviewed by this reviewer and the editor, and some incidents were excluded because the materials are no longer carried onboard or the possibility of such an inhalation has been eliminated through engineering safeguards. A total of 6 cases were considered representative of future risk on exploration missions. There are a number of studies looking at the incidence of toxic inhalation in terrestrial environments, but none of these were considered to be representative of spaceflight. The incidence of a toxic inhalation exposure is dependent on the materials used during the specific spaceflight and may vary widely from the estimated incidence here. The best case/worst case probabilities used data from the same study used to calculate the incidence. Of the 6 events that were included, one of them resulted in pulmonary edema and hospitalization was indicated. The BC/WC split of 83%/17% was estimated based on this analysis. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence, expert opinion, and the BC/WC definitions, and I am in agreement with their calculation. The Loss of crew life probabilities were all estimated to be zero based on the definition while all RTDC probabilities were estimated to be zero except for the untreated worst case. 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 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 is not dependent on mission phase but exposure to toxic materials may be greater during certain times such as the performance of scientific experiments or during maintenance/repair of onboard systems.

6. **Limitations**

- The estimated incidence is dependent on the specific materials that will be carried onboard. Current vehicle and habitat designs are still being finalized and tested. Depending on the exact nature of hazardous substances on board and the engineering safeguards built in, the incidence may vary widely from mission to mission.
- This CLIFF relies heavily on historical data of prior toxic chemical leaks or exposures. Each of these events underwent extensive and thorough evaluation to prevent future exposures and decrease the incidence in next generation vehicles. This theoretically should reduce the incidence of events within the DRM. However, without other information, incidence is dependent on historical data which will likely overestimate the risk of this condition.
- The severity of this condition is very mild for both the BC and WC scenarios and excludes patients suffering from respiratory failure which is a separate condition. Thus, all inhalational events with the capacity to cause symptoms were included in this condition which increases the calculated incidence.
- The best-case scenario for the condition “Respiratory Failure” includes minor respiratory support such as low flow oxygen. In the worst-case scenario for Toxic Inhalation, we include symptomatic treatment which may include oxygen for comfort. It is assumed that Toxic Inhalation does not include hypoxia requiring support.

Reviewed by:

David C. Hilmers