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In-Flight Carbon Dioxide Exposures and Related Symptoms: Association, Susceptibility, and Operational Implications

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ABSTRACT

The effects of ambient carbon dioxide and exposure limits have been well studied on Earth. However, informal crew reports on the International Space Station have suggested that astronauts are developing CO_2-related symptoms such as headache and lethargy at lower than expected CO_2 levels and that symptoms tend to resolve when CO_2 level is decreased. In-flight data to date support an association between elevated $ppCO_2$ and CO_2-related symptoms, but more research is needed to conclude causality. What appears to be increased CO_2 sensitivity in microgravity may be attributable to individual predisposition to CO_2 retention, adaptation to microgravity, and local fluctuations in CO_2 that are not measured by fixed sensors. A review of the current occupational exposure limits supports lowering of the permissible exposure limit for the ISS and beyond, although evidence-based limits for space flight have yet to be defined.

1. INTRODUCTION

Carbon dioxide is a natural product of metabolism. Each person exhales about 200 mL of CO_2 per minute at rest and may produce over 4.0 L/min at maximal exercise (Williams 2009). Left unchecked, CO_2 can accumulate quickly inside a closed environment. Other sources of CO_2 include combustion, decay of organic matter, and fire suppression systems.

On Earth, the ambient CO_2 concentration is about 0.03% by volume (0.23 mm Hg). In spacecraft, it is not practical to control CO_2 to such low levels. On the International Space Station (ISS), CO_2 levels are controlled primarily with the Vozdukh, a system of regenerable absorbers of CO_2 in the Service Module, and secondarily with the Carbon Dioxide Removal Assembly (CDRA) in the U.S. Laboratory; additionally, metal oxide (MetOx) and expendable lithium hydroxide (LiOH) canisters are available as backup. CO_2 concentrations in spacecraft are typically about 0.5±0.2% (3.8±1.5 mm Hg, or 2.3 to 5.3 mm Hg), with large fluctuations occurring over hours to days (James 2007). The highest $ppCO_2$ recorded in a U.S. spacecraft was 14.9 mm Hg on Apollo 13 (Michel 1975).

Several important physiological processes in the human body are modulated by CO_2. When blood CO_2 levels rise, chemoreceptors in the carotid and aortic bodies quickly trigger various centers in the medulla to send signals to the intercostal muscles, diaphragm, and sinoatrial node to increase minute ventilation and heart rate to enhance the body's elimination of CO_2. Hypercapnia also stimulates vasodilation of cerebral blood vessels, increase of cerebral blood flow, and elevation of intracranial pressure, presumably leading to headache, visual disturbance, impaired mental function, and other central nervous system (CNS) symptoms. Sliwka et al. (1998) reported that cerebral blood flow velocity in the middle cerebral artery increased by 35% on transcranial Doppler when subjects were exposed to chronic low concentrations of CO_2, and headache complaints were more frequent during the early days of exposure to 1.2% CO_2 (9 mm Hg).

Physiological tolerance time for various CO_2 concentrations and acute health effects of exposure to high concentrations of CO_2 are summarized in Table 1. Briefly, headache and exertional dyspnea begin to develop after an individual has been exposed to 2% CO_2 (15 mm Hg) for several hours. Sweating and dyspnea at rest may be seen after being exposed to 3% (23 mm Hg) CO_2 for one hour. Dizziness, lethargy, and uncomfortable dyspnea may develop within a few minutes of exposure to 4-5% (30-38 mm Hg) CO_2. Still higher CO_2 concentrations will cause unconsciousness, muscle twitching, convulsions, and eventually death (EPA 2000, Wong 1996).

Over the years, anecdotal evidence has suggested that ISS crewmembers are developing CO_2-related symptoms such as headache and lethargy at lower than expected CO_2 levels, and that symptoms tend to resolve when spacecraft $ppCO_2$ is decreased. These observations have raised a number of questions. Is CO_2 the cause of these symptoms? Is CO_2 sensitivity increased in microgravity? Are there individual differences in susceptibility to CO_2-related effects? What should operational exposure limits be? As the ISS transitions from assembly to laboratory operations, and as design decisions continue to be made in the Constellation program, it is important to address these questions. The purpose of this white paper is to provide an overview of suspected CO_2 toxicity in microgravity and evaluate whether current operational limits are appropriate. This paper is divided into four sections: 1) a summary of past efforts to correlate symptoms with elevated CO_2 levels; 2) a literature review to examine the latest data related to CO_2 susceptibility; 3) a review of the current occupational limits and flight rules for CO_2 exposure; and 4) a discussion about operational implications.

2. SYMPTOMS AND CO_2

First, the following are reviewed: CO_2-related symptoms reported on the ISS, in-flight data to date, and efforts to correlate symptoms with CO_2 levels. For reference, Table 2 summarizes key CO_2 concentrations discussed in this paper.

2.1. Crew Reports of Symptoms

One of the first reports of possible CO_2 toxicity on the ISS came from the ISS-2A crew. Headache was reported on two occasions: one while crewmembers were working inside a confined space where there was reduced air flow, and the other when all of the crewmembers were gathered in a single location. Both times, crewmembers described their symptoms as similar to those they experienced when they were intentionally exposed to excess CO_2 during ground training (James 2007). Similarly, the crew of STS-123 reported ill effects and feeling of confinement that were attributed to CO_2 overexposure when the entire crew tried to gather together for a meal (ISS Program MIOCB 2009).

Other informal reports of "CO_2-like symptoms" on board the ISS were recorded on STS-112/ISS-9A, STS-113/ISS-11A, and Expedition 6. The cases were analyzed in detail by Felker (2003) and summarized here:

- STS-112/ISS-9A: The crew requested an unplanned Shuttle LiOH canister installation. At the time, the ISS $ppCO_2$ was 2.7 mm Hg, and both the ISS and Shuttle $ppCO_2$ readings on that day were low (mostly less than 4 mm Hg and never exceeding 6 mm Hg); as a result, the LiOH was not installed. It was not until several months after the mission when three of the Shuttle crewmembers and one ISS crewmember reported their headaches as the problem. The headaches were alleviated by acetaminophen and donning of EMUs (thus breathing 100% oxygen).

Interestingly, one crewmember who slept directly in a fan outlet draft did not get relief from the presumably improved air circulation.
- STS-113/ISS-11A: A Shuttle crewmember reported headache symptoms on the same day as elevated CO_2 levels up to 7.5 mm Hg were recorded before change out of the CDRA. It was assumed that installation of the LiOH in the interim alleviated the symptoms. There were no further reports after the CDRA was reactivated.
- Expedition 6: There were two separate reports of lethargy, malaise, listlessness, and fatigue when $ppCO_2$ rose above 4 mm Hg but remained within flight rule limits. The crew noted that these symptoms subsided within minutes of reduction of $ppCO_2$ to the 2 mm Hg range or when they breathed 100% O_2 in an EMU suit. Furthermore, the crew felt better and reported improved performance when CO_2 levels were low.

2.2. In-Flight CO_2 Data to Date

Several studies have been conducted to measure CO_2 levels on board the Space Shuttle and ISS.

Space Shuttle. On STS-122 and STS-123, under Detailed Test Objective (DTO) #853, CO_2 readings were taken using portable Carbon Dioxide Monitors (CDM) in addition to the Shuttle's single Infrared Carbon Dioxide ($IRCO_2$) sensor. The CDMs were placed at specific locations on the middeck during crew sleep periods. Figure 1 shows $ppCO_2$ versus time for each mission. The CDM data matched closely with the $IRCO_2$ data, suggesting that middeck CO_2 levels were consistent with what the only CO_2 sensor on the Shuttle was measuring. All $ppCO_2$ readings were below the flight rule limit of 7.6 mm Hg. However, this DTO was run only during crew sleep periods and did not measure CO_2 concentrations when crewmembers were more metabolically active. Furthermore, because the CDMs were not placed near the crew's sleep stations, there was no information about potential local CO_2 pockets around the crewmembers, and the data might not have reflected the crew's actual CO_2 exposures (Wu 2009).

International Space Station. SDTO #25007 was proposed by NASA flight surgeons to determine the spatial and temporal variations in $ppCO_2$ experienced by astronauts during a work day and during exercise on the ISS using a CDM worn by two crewmembers. Figure 2 shows the CDM data plotted along with data from the Major Constituent Analyzer (MCA), which was the primary instrument on the ISS for monitoring major atmospheric constituents. During both sessions, the CDM data generally matched closely with the MCA data, and all measurements remained below 3.0 mm Hg. No headaches were reported in either session. However, periodic spikes, representing local increases in $ppCO_2$, were observed in the CDM data especially during exercise, suggesting that CO_2 could accumulate in the crew's breathing zone (James 2007). The increased exposures appeared to be brief given the sharpness of the spikes (Wu 2009).

On STS-127/2JA, EVA-3 was terminated early due to concern about a failing LiOH canister and rising CO_2 levels. CO_2 concentrations remained below flight limits and peaked at 3 mm Hg. The EVA astronaut did not develop any symptoms of hypercapnia (Gebhardt 2009).

2.3. Correlation of Symptoms with CO_2 Levels

In an effort to correlate reported headaches with CO_2 concentrations, the Exploration Medical Capability (ExMC) group analyzed headache occurrences identified in the Longitudinal Study of Astronaut Health (LSAH) and on Expeditions 12, 13, 14, 15, and 17 (Wu 2009). For each of the eight reported headaches, MCA and CDM data were obtained spanning the two-week period from one week before the reported event to one week after, including the day of headache occurrence (see Figure 3).

Analysis of $ppCO_2$ on days where there was a headache event compared to other days in each two-week period (see Figure 4) showed no statistically significant difference between the two groups ($p = 0.62$ by Student's t-test). The rate of change in $ppCO_2$ was also considered. While the majority of data showed a rising trend in CO_2 concentration preceding the onset of headache, the rate of change itself was unlikely to account for headache occurrence given the following observations. First, during the two-week period around GMT 2005-175, there was a consistent, approximately 0.044 mm Hg/hour rise in $ppCO_2$, yet only one headache event was reported (Wu 2009). Second, $ppCO_2$ appeared to be trending downward when the headache event was reported on GMT 2007-282.

This study had a number of limitations. First, the headache reports lacked temporal resolution, since only the date of each headache occurrence was known, so it was difficult to correlate a CO_2 spike with a headache event when the exact timing of the headache was unknown. Second, although there was good correlation between CO_2 data collected by the MCA and data collected by the CDM ($r^2 = 0.98$, see Figure 5), most of the CO_2 data were collected by the MCA, which monitored ambient CO_2 levels for the entire cabin at fixed locations and lacked spatial resolution. Thus, local pockets of CO_2 near the crew possibly causing the headaches could not be ruled out.

Carr (2006) retrospectively analyzed crew symptoms reported during private medical conferences (PMC) on Expeditions 1 through 7 and $ppCO_2$ measurements obtained in the U.S. Laboratory Module during those 16 unique PMC periods. Headache was the most commonly reported symptom; other symptoms reported included lethargy, mental slowness, emotional irritation, and sleep disruption. Symptoms were alleviated by the use of the CDRA, increased ventilation, exercise, use of 100% O_2 in the EMU, sleeping in a lower $ppCO_2$ environment, and breathing exercises that were part of a flight experiment. Symptoms were found to be correlated with elevations in mean $ppCO_2$ averaged over 1 day, 3 days, and 7 days (excluding flight day <7 due to possible confounding by acute physiological adaptation to microgravity), with all p values less than 0.05. Sensitivity and specificity analysis using receiver operating curves showed that a $ppCO_2$ threshold of 4.9 mm Hg yielded a positive predictive value of 50% and negative predictive value of 90% for CO_2-related symptoms.

While these anecdotes and studies support an association between elevated $ppCO_2$ and CO_2-related symptoms, causality remains to be proven. Not enough information about local CO_2 exposures is known. Furthermore, other atmospheric contaminants may be present and have not been taken into account. For example, elevated carbon monoxide and hydrogen cyanide, which are often products of incomplete combustion or off-gassing from plastics, can also cause headache, irritability, fatigue, and dyspnea (OSHA 2009).

3. CO_2 SUSCEPTIBILITY

Both individual and environmental factors may contribute to space crews' susceptibility to CO_2 effects in microgravity. Some individuals appear to be more prone to CO_2 retention and therefore develop symptoms at lower CO_2 levels. Differences in physiological adaptation to microgravity may also be a factor in individual susceptibilities. Nonetheless, high enough levels of CO_2 will cause toxicity in all crewmembers. While ambient spacecraft CO_2 levels have generally remained below flight limits, local elevations not measured by fixed sensors may be responsible for the development of CO_2-related symptoms.

3.1. CO_2 Retention

Hypercapnia is a well-known cause of headaches in divers, some of whom appear to be more susceptible to CO_2 retention. Several factors have been implicated in CO_2 retention in divers, including increased hydrostatic pressure across the chest wall, increased work of breathing due to high gas density at depth, conditioned behavior such as "skipped breathing" to conserve air, and hypoventilation due to low respiratory CO_2 sensitivity (Pendergast 2006, Cheshire 2001, Lanphier and Bookspan 1999). Of these, low CO_2 sensitivity is likely the only factor applicable to space flight.

In a study to investigate respiratory muscle training on respiratory CO_2 sensitivity in healthy divers, Pendergast et al. (2006) measured CO_2 sensitivity by having subjects breathe in and out of a spirometer filled with 91.5% O_2 and 8.5% CO_2 and recording their ventilatory response. Of the 35 subjects, 10 (29%) had low CO_2 sensitivity (<2 L/min/mm Hg CO_2), 19 (54%) had normal CO_2 sensitivity (2-4 L/min/mm Hg CO_2), and 6 (17%) had high CO_2 sensitivity (>4 L/min/mm Hg CO_2). If these data could be extrapolated to the astronaut population, at least one crewmember in a crew of six would be expected to have low CO_2 sensitivity and theoretically increased susceptibility to CO_2 retention leading to hypercapnia and potentially symptoms.

3.2. Adaptation to Microgravity

In his analysis, Carr (2006) found a stronger correlation between CO_2-related symptoms and elevated $ppCO_2$ when data before flight day seven were excluded, but statistically significant differences were still present in the 1-day and 3-day mean values for all days with symptom reports compared to those without. He also noted that a veteran astronaut had reported a headache within the first seven days of flight and described it as "'the usual experience' of adaptation to the space environment."

One of the most immediate physiological changes encountered in microgravity is cephalad fluid shift. Increased fluid volume in the head and neck may increase intracranial pressure (ICP) and reduce upper airway caliber (Elliott 2001). Since ICP has not been directly measured in space, data on ICP-related effects have mostly been obtained during head-down-tilt (HDT) bed rest studies that simulate fluid shift seen in microgravity. In one study, subjects underwent three days each of horizontal bed rest and 6 degrees of HDT in a randomly chosen order, and headache was reported only during the HDT condition (Styf 2001). Additionally, reduced airway caliber may promote air trapping in the lungs and result in CO_2 retention. In short, cephalad fluid shifting in microgravity could potentiate CO_2-mediated cerebral vasodilation, resulting in CNS symptoms at lower than expected CO_2 levels. Whether this is indeed happening in space remains to be studied.

3.3. Local Fluctuations in CO_2 Levels

Because air convection is significantly reduced in microgravity, local pockets of CO_2 may form around sources of CO_2 such as the nose and mouth. A computational fluid dynamics analysis revealed that without adequate ventilation, $ppCO_2$ could rise above 9 mm Hg within 10 minutes around a sleeping crewmember's mouth and chin (Son 2002).

Few investigations to date have measured true CO_2 exposures. The Station's MCA and the Shuttle's $IRCO_2$ have fixed locations that do not necessarily reflect local CO_2 levels around crewmembers as they move inside the crew compartments. Even the CDMs may not measure truly local $ppCO_2$, unless the monitors are worn by the crewmembers close to their breathing zone as in SDTO #25007. Generally, the CDMs are placed on cabin walls and not directly next to the crew due to concern about internal pump noise and potential for low battery alarm (Hayley 2008), and only during planned experiments or when the MCA is nonoperational. In other words, CDM data may not be representative of what the crew truly experiences. What little data are available already show fluctuations in the CDM $ppCO_2$ readings that are not detected by the MCA, especially during exercise as recorded in SDTO #25007. Local effects have yet to be characterized during known rapid changes in $ppCO_2$ that the MCA can measure, e.g., when a CO_2 scrubber is being changed out or when one vehicle docks with another that has a different level of CO_2 (James 2007).

All in all, as every report to date on this topic has pointed out, more data are needed to further our understanding of individual and environmental factors that contribute to CO_2-related symptoms in microgravity. It may be that certain individuals are more susceptible to CO_2 retention and increased ICP, but until true exposure data are available to correlate symptoms and $ppCO_2$, no conclusion can be drawn at this time about CO_2 susceptibility in space flight.

4. REVIEW OF CO_2 LIMITS AND FLIGHT RULES

Despite limited data, the flight surgeons have empirically lowered their threshold for action to 5 mm Hg due to concern about headache and other symptoms being linked to CO_2 levels. Before evaluating this new limit, the current occupational exposure limits, Spacecraft Maximum Allowable Concentrations, and flight rules are reviewed for historical perspective.

4.1. Occupational Exposure Limits

The Occupational Safety and Health Administration (OSHA) sets the following permissible exposure limits (PEL) (OSHA 1990):

- Final Rule Limit: 10,000 ppm (1% or 7.5 mm Hg) Time Weighted Average (TWA) over a work shift up to 8 hours per day, 40 hours per week.
- Transitional Limit: 5,000 ppm (0.5% or 3.8 mm Hg).

- Short-Term Exposure Limit: 30,000 ppm (3% or 23 mm Hg) TWA over a 15-minute period.

The National Institute for Occupational Safety and Health (NIOSH), which conducts research and advises OSHA, recommends an additional "immediately dangerous to life or health" exposure limit of 40,000 ppm (4% or 30 mm Hg).

The current flight rules for the ISS, to be discussed in the next section, are partly derived from these exposure limits. Of note, the most recent edition of the NIOSH guidelines (NIOSH 2005) has lowered the recommended exposure limit to 5,000 ppm (0.5% or 3.8 mm Hg) TWA over 10 hours per day, 40 hours per week.

4.2. Spacecraft Maximum Allowable Concentrations

The original spacecraft maximum allowable concentrations (SMAC) for CO_2 were set by a subcommittee of the National Research Council and published by Wong (1996) after an extensive review of all known effects of CO_2 exposures. The most recent revision by James (2008), summarized in Table 3, raised the 1-hour SMAC for CO_2 to 2.0% (15 mm Hg) from 1.3% (10 mm Hg) to reflect new aggregate data suggesting that any occurrence of mild headache or hyperventilation would be easily tolerated for one hour with insignificant effect on crewmember performance. The 24-hour and 7 to 180-day SMAC remained 1.3% (10 mm Hg) and 0.7% (5 mm Hg), respectively. A new 1,000-day SMAC was set at 0.5% (3.8 mm Hg), a conservative level designed to provide a larger safety margin on Exploration Class missions, which would have chronic exposure and limited resupply and rescue capability.

4.3. Flight Rules

The ISS flight rules pertaining to CO_2 were partly derived from SMACs, NIOSH guidelines, and OSHA standards. Separate flight rules govern the ISS and extravehicular activity spacesuits, which are two-gas and one-gas environments, respectively (NASA JSC 2008).

Station Operations. Flight Rule B13-53 ("PPCO_2 Constraints") prescribes required actions when station ppCO_2 levels approach or exceed the permissible exposure limit of 7.6 mm Hg.

- If ppCO_2 levels average higher than 5.3 mm Hg over 5 days or 6.0 mm Hg over 1 day, the flight surgeon must be consulted when planning crew activities.
- If ppCO_2 levels reach or exceed 7.6 mm Hg, measures must be taken to lower the ppCO_2 to permissible levels per Flight Rule B17-5 ("CO_2 Partial Pressure Limits and Actions"), which details specific actions to troubleshoot and scrub CO_2. The same corrective actions are required if ppCO_2 is 4.5 mm Hg or greater and CO_2-related symptoms not attributed to another cause are present.
- *Off-nominal situation:* Immediate action to minimize adverse CO_2 effects on the crew must be taken at CO_2 levels of 10 to 15 mm Hg. The gas environment is scrubbed down to allowable CO_2 levels. If signs of illness develop, the crew must use individual breathing devices (IBD). If the ppCO_2 remains above 7.6 mm Hg or if the IBDs get expended, the crew must evacuate the affected area. Exposure to CO_2 levels of 10 to 15 mm Hg are limited to 8 hours or less.
- *Emergency situation:* Immediate action with the highest priority to prevent crew exposure must be taken at CO_2 levels of 15 to 20 mm Hg. The crew is to use IBDs when performing repair

operations, scrub down the gas environment, and evacuate the affected area if $ppCO_2$ remains higher than 15 mm Hg or if IBDs become expended.

Extravehicular Activity. EVA is governed by two sets of flight rules, depending on whether the Extravehicular Mobility Unit (EMU) or the Orlan spacesuit is used.

Flight Rule B13-251 ("EMU PPO_2 and $PPCO_2$ Constraints") requires $ppCO_2$ in the EMU to be maintained below the physiological limit of 15 mm Hg. EVA is to be terminated if:

- Symptoms of CO_2 toxicity develop; or
- The EMU Caution and Warning System reading exceeds 12.4 mm Hg in the enhanced (i.e., pressure compensated) configuration or 8.0 mm Hg in the baseline configuration.

In case of loss of CO_2 sensor, the flight surgeon may request physiological status checks to evaluate the crew for symptoms of CO_2 toxicity. Additionally, Flight Rule B15-110 ("EMU Consumables for ISS") requires the extravehicular crew to terminate EVA under these situations:

- When EMU data are available to Mission Control: $ppCO_2$ reaches 2.75 mm Hg (if LiOH is used for scrubbing) or 3.2 mm Hg (if MetOx is used) and is increasing; or
- When EMU data are not available to Mission Control: $ppCO_2$ reaches 8.0 mm Hg (pressure-compensated) or 3.0 mm Hg (uncompensated).

In contrast, Flight Rule B13-252 ("Orlan PPO_2 and $PPCO_2$ Constraints") sets the EVA-termination limit to be 20 mm Hg during activity or 10 mm Hg during rest time. The discrepancies between EMU CO_2 limits and Orlan CO_2 limits were discussed during a Medical Operations EVA Integrated Product Team meeting and deemed to have little safety impact (Dervay 2000).

To date, ISS missions have operated within these constraints. However, symptom reports have emerged over the years that suggest an increased sensitivity to CO_2 in microgravity and that lower limits may be needed to prevent CO_2 toxicity. Furthermore, recently published data and guidelines as discussed in the preceding sections have yet to be incorporated into the flight rules.

5. OPERATIONAL IMPLICATIONS

After a review of these data and guidelines, it appears logical to lower flight limits for CO_2 exposure. Considering that NIOSH now recommends a lower CO_2 exposure limit and that crewmembers are becoming symptomatic before $ppCO_2$ reaches the current 7.6 mm Hg limit, which is also the proposed CO_2 limit for the Constellation EVA suit (Alexander 2009), decreasing the operational exposure limit to 3.8 mm Hg (0.5%) as recommended by NIOSH makes sense and would be in agreement with the new long-term SMAC.

Assuming that the data from the ExMC study are representative of $ppCO_2$ measurements on the ISS, threshold analysis reveals that only 46% of the measured CO_2 levels would fall below the permissible exposure limit if it were lowered to 3.8 mm Hg. Thus, over half of the time, there would need to be increased CO_2 scrubbing using the Vozdukh, CDRA, and backup canisters, translating to increased demand for power and consumables. Figure 6 provides a graphical representation of various threshold levels and the resulting "compliance" rate. In addition to increasing resource consumption, a lower permissible exposure limit could divert the crew from achieving mission objectives if active measures are required to decrease $ppCO_2$ to acceptable levels, or if planned activities are terminated early as in the case of EVA 3 on STS-127/2JA.

On the other hand, one may argue for an even more conservative limit on the ISS, since the current occupational exposure limits are based on time-averaged exposures of up to 8 hours per work day according to OSHA (10 hours per NISOH) or 40 hours per work week, which is significantly less than the 24 hours per day or 168 hours per week that a station crew spends in space. To adjust the exposure limit, OSHA's formula for "unusual work schedules" for chemicals without cumulative effects (Paustenbach 2000), of which CO_2 is assumed to be one, may be used:

$$\begin{aligned}\text{Equivalent PEL} &= \text{8-hour PEL} \times (\text{8 hours / hours of exposure per day}) \\ &= 10{,}000 \text{ ppm} \times (\text{8 hours / 24 hours}) \\ &= 3{,}333 \text{ ppm} = 2.5 \text{ mm Hg time-weighted average}\end{aligned}$$

Striking a balance between such stringent occupational exposure limits and practical considerations, the flight surgeons' empiric threshold of 5 mm Hg (about 0.7%) appears to be a good compromise until more data become available. Ninety percent of the CO_2 measurements in the ExMC study fall below 5 mm Hg, which is very close to the 4.9 mm Hg threshold that Carr (2006) found in his sensitivity and specificity analysis of PMC data, and 5 mm Hg is also the threshold below which chronic exposure reportedly has minimal effect on human performance or mood according to a joint NASA-ESA-DARA study (Manzey 1998). It would be very informative to analyze resource consumption and symptom reports before and after the implementation of this threshold to evaluate its operational impact.

Similarly, the off-nominal $ppCO_2$ level and emergency $ppCO_2$ level, currently defined to be 15 mm Hg and 20 mm Hg respectively, are based on old SMACs. These levels may also need to be adjusted if the evidence demonstrates that adverse physiological changes or decrements in performance begin to develop at lower CO_2 concentrations in space.

Clearly, more research is needed. Investigations that may elucidate the role of CO_2 in microgravity include the following:

- Wearable CO_2 monitors to determine the true local CO_2 environment around each crewmember, with concomitant measurement of trace atmospheric contaminants.
- Detailed records of crew symptoms, including time of onset and offset, alleviating and exacerbating factors, and description (e.g., whether it is like "the usual" headache associated with the first seven days of flight). Even if the symptoms are not reported during PMCs, crewmembers should be encouraged to record details about their symptoms.
- Data mining of electronic medical records to obtain existing symptom data that have yet to be analyzed.
- Correlation of mission timeline records of crew activities that likely increase local CO_2 levels—e.g., working in a confined space behind panels, crowding inside small compartments for public outreach activities, and CO_2 scrubber change outs—with CO_2 measurements and symptom reports.

- Analysis of astronaut CO_2 exposure training data to correlate CO_2 sensitivity on the ground with symptom incidence in microgravity.
- Indirect measurements of intracranial pressure (e.g., transcranial Doppler to assess blood flow in the middle cerebral artery, or ultrasound measurement of optic nerve sheath diameter) in microgravity to evaluate the contribution of cephalad fluid shift to CO_2-related symptoms.
- Modeling of cardiopulmonary and cerebral responses to varying degrees of hypercapnia in the context of microgravity.

Once the association between CO_2 and symptoms on the ISS is better understood, one can then refine the flight exposure limits based on the data. Also, if the large swings in CO_2 level seen during scrubber change outs could be engineered out or reduced, it may be possible to prevent some of the CO_2-related symptoms and provide crews with additional protection from excessive CO_2 exposure.

6. CONCLUSION

Several investigations have begun to evaluate the association between CO_2 levels and reports of CO_2-related symptoms such as headache and lethargy. However, there are not enough data to conclude causality. Furthermore, although the literature supports the observation that certain individuals are more susceptible to the effects of CO_2 and that adaptation to microgravity may potentiate the effects of CO_2, it remains unclear whether CO_2 sensitivity is indeed increased in microgravity, given temporal and spatial limitations in the CO_2 data as well as crew symptom reports. Given our current knowledge about crew symptoms and revised occupational exposure limits and SMACs, it appears reasonable to maintain a lower $ppCO_2$ limit than what is currently set for ISS operations while heeding flight constraints. More research is needed to expand the evidence base for CO_2 exposures and symptoms in microgravity to optimize in-flight exposure limits on the ISS and future programs.

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7. REFERENCES

Alexander D, Wu J. Constellation EVA Carbon Dioxide Limit. Internal Presentation to the Space Medicine Configuration Control Board, 17 Sep 2009.

Carr CE. Impact of moderate elevations in CO_2 on astronauts during long-duration spaceflight on the International Space Station. Internal Report, 2006.

Cheshire WP Jr, Ott MC. Headache in divers. Headache. 2001 Mar;41(3):235-47.

Dervay J. Med Ops EVA-IPT Meeting Minutes. Houston, TX, 31 Oct 2000.

Elliott AR, Shea SA, Dijk DJ, Wyatt JK, Riel E, Neri DF, Czeisler CA, West JB, Prisk GK. Microgravity reduces sleep-disordered breathing in humans. Am J Respir Crit Care Med. 2001 Aug 1;164(3):478-85.

Environmental Protection Agency. Carbon dioxide as a fire suppressant: examining the risks. Report EPA430-R-00-002, 2000.

Felker P. Assessment of crew reports on ISS carbon dioxide symptoms. Internal Report, 2003.

Gebhardt C. EVA-3 terminated due to LiOH concern, NASASpaceflight.com, 22 July 2009. Accessed on 8 Oct 2009 at http://www.nasaspaceflight.com/2009/07/sts-127-begins-eva-3-dat-present-tps-clearance-reports/.

Hayley L. STS-122 Shuttle Detailed Test Objective 853 results using Shuttle Carbon Dioxide Monitor (SCDM). Internal Presentation, March 2008.

Hayley L. STS-123 Shuttle Detailed Test Objective 853 results using Shuttle Carbon Dioxide Monitor (SCDM). Internal Presentation, April 2008.

International Space Station Program Mission Integration and Operations Control Board (MIOCB). Interim Report Meeting Minutes, 9 July 2009, Houston, TX. Accessed on 1 Oct 2009 at http://iss-www.jsc.nasa.gov/nwo/ppco/cbp_miocb/bbt_docs/bbtcal/Minutes.6.09-Jul-2009.htm

James JT. The headache of carbon dioxide exposures. Society of Automotive Engineers. Paper No. 07ICES-42, 2007.

James JT. Carbon dioxide. In: National Research Council, Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol 5. Washington, DC: National Academy Press;2008:112-124.

Lanphier EH, Bookspan J. Carbon dioxide retention, Chap 6. In: Lundgren EG, Miller JN, editors. The Lung at Depth. New York: Marcel Dekker, 1999.

Manzey D, Lorenz B. Joint NASA-ESA-DARA Study. Part three: effects of chronically elevated CO_2 on mental performance during 26 days of confinement. Aviat Space Environ Med. 1998 May;69(5):506-14.

Michel EL, Waligora JM, Horrigan DJ, Shumate WH. Environmental factors. In: Johnston RS, Dietlein LF, Berry CA, editors. Biomedical Results of Apollo. NASA SP-368. Washington, DC; 1975.

NASA Johnson Space Center. ISS Generic Operational Flight Rules, Vol B. Houston, TX: 2008. Accessed on 9 Sep 2009 at http://mod.jsc.nasa.gov/Da8/rules/vol_b/rules.htm.

National Institute for Occupational Safety and Health. Occupational Health Guideline for Carbon Dioxide, Sep 1978. Accessed on 30 Sep 2009 at http://origin.cdc.gov/niosh/docs/81-123/pdfs/0103.pdf.

National Institute for Occupational Safety and Health. Pocket Guide to Chemical Hazards. NIOSH Publication 2005-149, 2005. Accessed on 30 Sep 2009 at http://www.cdc.gov/niosh/npg/npgd0103.html.

Occupational Safety and Health Administration. Carbon Dioxide in Workplace Atmospheres. Sampling and Analytical Methods, revised 1990. Accessed on 12 Oct 2009 at http://www.osha.gov/dts/sltc/methods/inorganic/id172/id172.html.

Occupational Safety and Health Administration. NIOSH/OSHA/DOE Health Guidelines, 2009. Accessed on 15 Oct 2009 at http://www.osha.gov/SLTC/healthguidelines/index.html.

Paustenbach DJ. The history and biological basis of occupational exposure limits. In: Harris RL, editor. Patty's Industrial Hygiene, Vol. 3, 5th edition. New York: John Wiley & Sons, Inc., 2000.

Pendergast DR, Lindholm P, Wylegala J, Warkander D, Lundgren CEG. Effects of respiratory muscle training on respiratory CO_2 sensitivity in SCUBA divers. Undersea Hyperb Med. 2006 Nov-Dec;33(6):447-53.

Sliwka U, Krasney JA, Simon SG, Schmidt P, Noth J. Effects of sustained low-level elevations of carbon dioxide on cerebral blood flow and autoregulation of the intracerebral arteries in humans. Aviat Space Environ Med. 1998 Mar;69(3):299-306.

Son CH, Zapata JL, Lin CH. Investigation of airflow and accumulation of carbon dioxide in the Service Module crew quarters. Society of Automotive Engineers. Technical Paper No. 2002-01-2341, 2002.

Styf JR, Hutchinson K, Carlsson SG, Hargens AR. Depression, mood state, and back pain during microgravity simulated by bed rest. Psychosom Med. 2001 Nov-Dec;63(6):862-4.

Williams WJ. Physiological Responses to Oxygen and Carbon Dioxide in the Breathing Environment. National Institute for Occupational Safety and Health Public Meeting slides, 17 Sep 2009, Pittsburgh, PA. Accessed on 30 Sep 2009 at http://www.cdc.gov/niosh/npptl/resources/certpgmspt/meetings/09172009/pdfs/9CO202PresentWJW.pdf.

Wong KL. Carbon dioxide. In: National Research Council, Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol 2. Washington, DC: National Academy Press; 1996;105-188.

Wu J. In-Flight Carbon Dioxide Data Collection Efforts. Internal Report, 2009.

8. TABLES AND FIGURES

Table 1. Physiological tolerance time for various CO_2 concentrations and acute health effects of high concentrations of CO_2.

PHYSIOLOGICAL TOLERANCE			ACUTE HEALTH EFFECTS	
$ppCO_2$		Maximum Exposure Limit (min)	Duration of Exposure	Effects
mm Hg	%			
3.8	0.5%	Indefinite		
7.5	1.0%	Indefinite		
11	1.5%	480		
15	2.0%	60	Several hours	Headache, dyspnea upon mild exertion
23	3.0%	20	1 hour	Headache, sweating, dyspnea at rest
30	4.0%	10	(4-5%) Within few minutes	Headache, dizziness, increased blood pressure, uncomfortable dyspnea
38	5.0%	7		
45	6.0%	5	1-2 minutes ≤16 minutes Several hours	Hearing, visual disturbances Headache, dyspnea Tremors
53	7.0%	<3	(7-10%) Few minutes 1.5 minutes to 2 hours *9% for 5 minutes*	Unconsciousness, near-unconsciousness Headache, increased heart rate, shortness of breath, dizziness, sweating, rapid breathing *Lowest published lethal concentration*
68	9%	N/A		
75	10%	N/A	(>10-15%) 1 minute to several minutes	Dizziness, drowsiness, severe muscle twitching, unconsciousness
113	15%	N/A		
128	17%	N/A	(17-30%) Within 1 minute	Loss of controlled and purposeful activity, unconsciousness, convulsions, coma, death

Adapted from EPA 2000.

Table 2. Key CO_2 concentrations discussed in this paper. 1% = 7.5 mm Hg.

% CO_2	**$PPCO_2$ (mm Hg)**	**Note [Reference]**
0.03%	0.23	Ambient outdoor CO_2 level on Earth
	2	Relief of symptoms on Expedition 6 [1]
0.3-0.7%	2.3-5.3	Typical spacecraft CO_2 concentrations [2]
0.5%	3.4	**New NIOSH Recommended Exposure Limit** [3]
	>4	Lethargy, malaise, listlessness, and fatigue on Expedition 6 [1]
	4.9	Derived threshold corresponding to 90% negative predictive value for CO_2-related symptoms [4]
	5	Safe chronic CO_2 level in terms of performance [5] **Empiric threshold established by flight surgeons**
	2.7 to <6	Headaches on STS-112/ISS-9A [1]
	Up to 7.5	Headache on STS-113/ISS-11A [1]
1%	7.5	**NIOSH Permissible Exposure Limit** [6]
	8	**EMU EVA termination limit** with baseline Caution and Warning System [7]
1.2%	9	Slight performance decrement after chronic exposure [5]
	10	**Orlan EVA termination limit** with crew at rest [8]
	12.4	**EMU EVA termination limit** with enhanced Caution and Warning System [7]
1.99%	14.9	Maximum CO_2 concentration on Apollo 13 [9]
2%	15	Headache, exertional dyspnea start [10] **ISS Off-Nominal $ppCO_2$ Level** [11]
	20	**ISS Emergency $ppCO_2$ Level** [11] **Orlan EVA termination limit** [8]
3%	23	Sweating, resting dyspnea start [10] **NIOSH Short-Term Exposure Limit** [3]
4%	30	**NIOSH Immediately Dangerous to Life or Health limit** [3]
4-5%	30-38	Dizziness, lethargy, uncomfortable dyspnea start [10]

References

[1] Felker 2003
[2] James 2007
[3] NIOSH 2005
[4] Carr 2006
[5] Manzey 1998
[6] NIOSH 1978
[7] Flight Rule B13-251
[8] Flight Rule B13-252
[9] Michel 1975
[10] EPA 2000
[11] Flight Rule B13-53

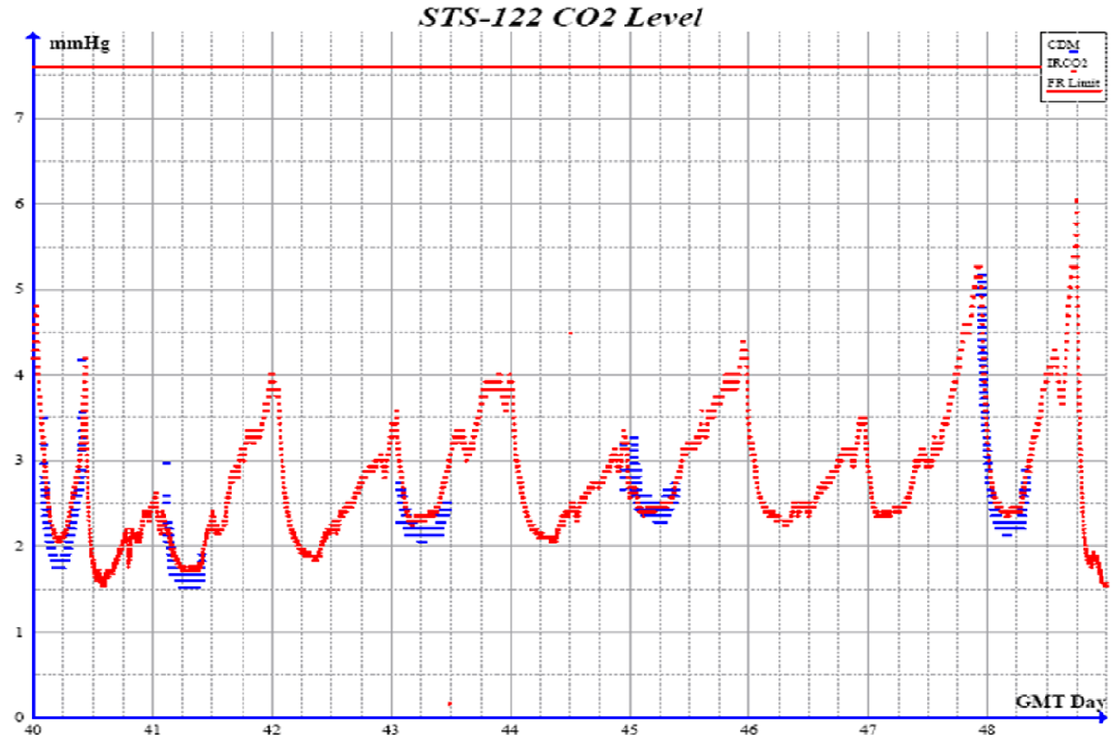
Table 3. Spacecraft Maximum Allowable Concentrations (SMACs) for CO_2

Exposure Time	SMAC (%)	Equivalent SMAC (mm Hg)
1 hour	2.0%	15
24 hours	1.3%	10
7 to 180 days	0.7%	5
1000 days	0.5%	4

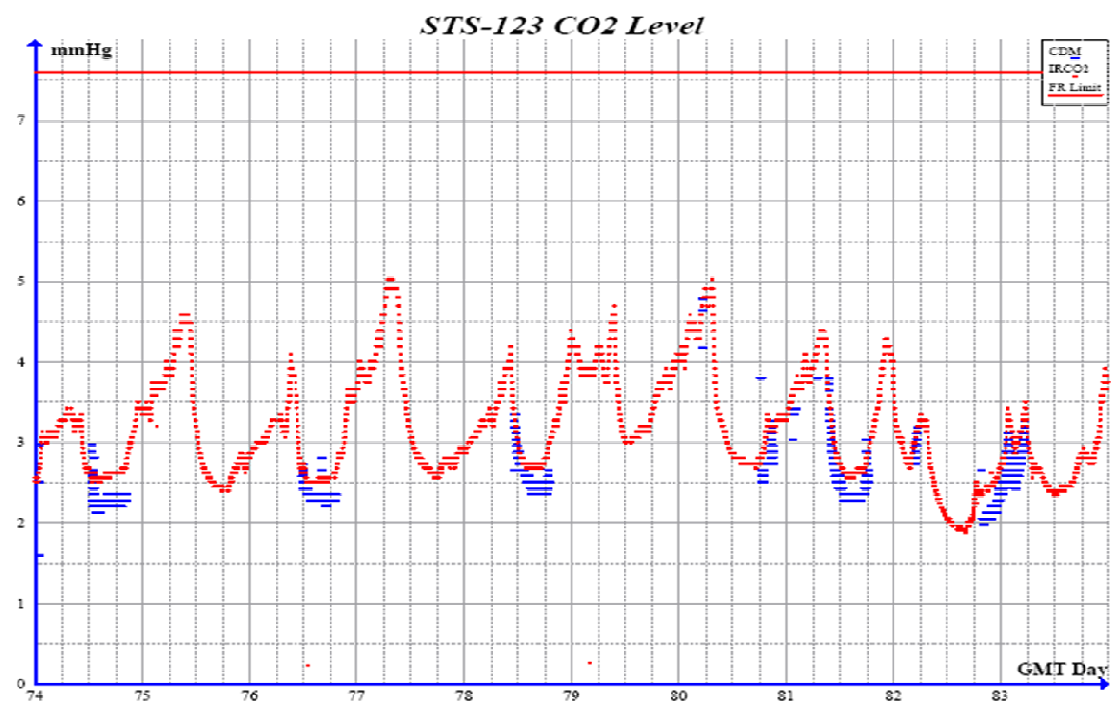
Reference: James 2008

Figure 1. CO_2 concentrations on board the Shuttle measured by the Carbon Dioxide Monitor (CDM) and the $IRCO_2$ sensor on STS-122 (1A) **and STS-123** (1B) [Shuttle DTO 853]**.**

(1A)



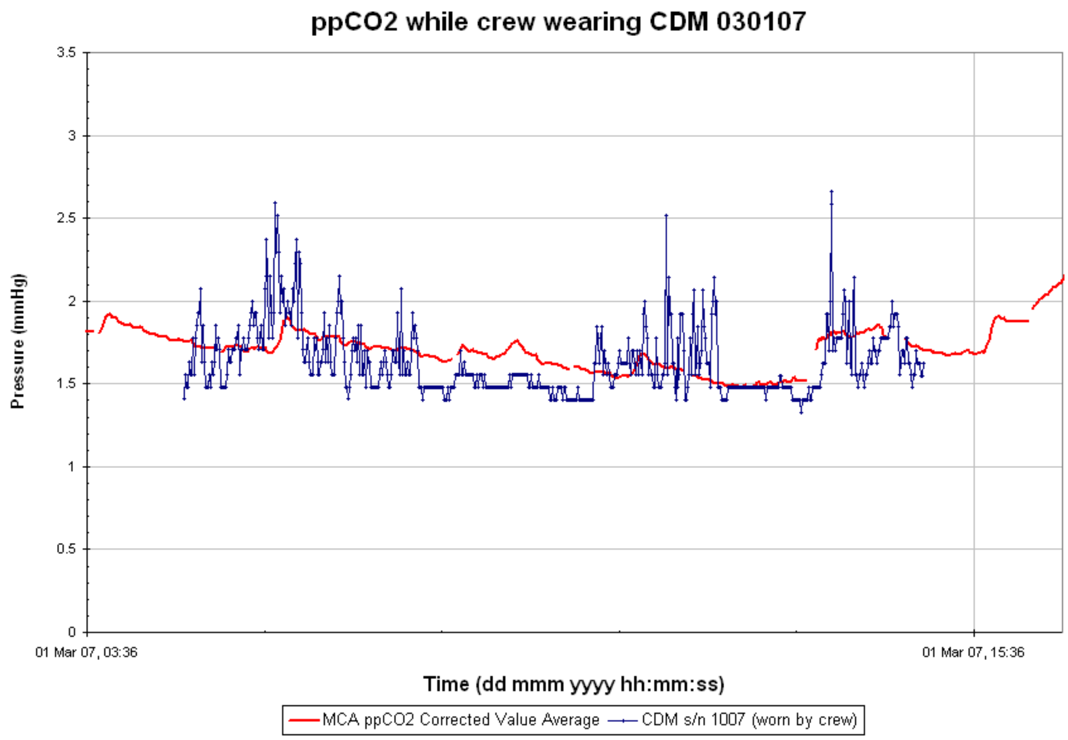
(1B)



Reference: Hayley 2008.

Figure 2. CO_2 concentrations on board the ISS during a work day (2A) **and during exercise** (2B)**.** (SDTO #25007)

(2A)



(2B)

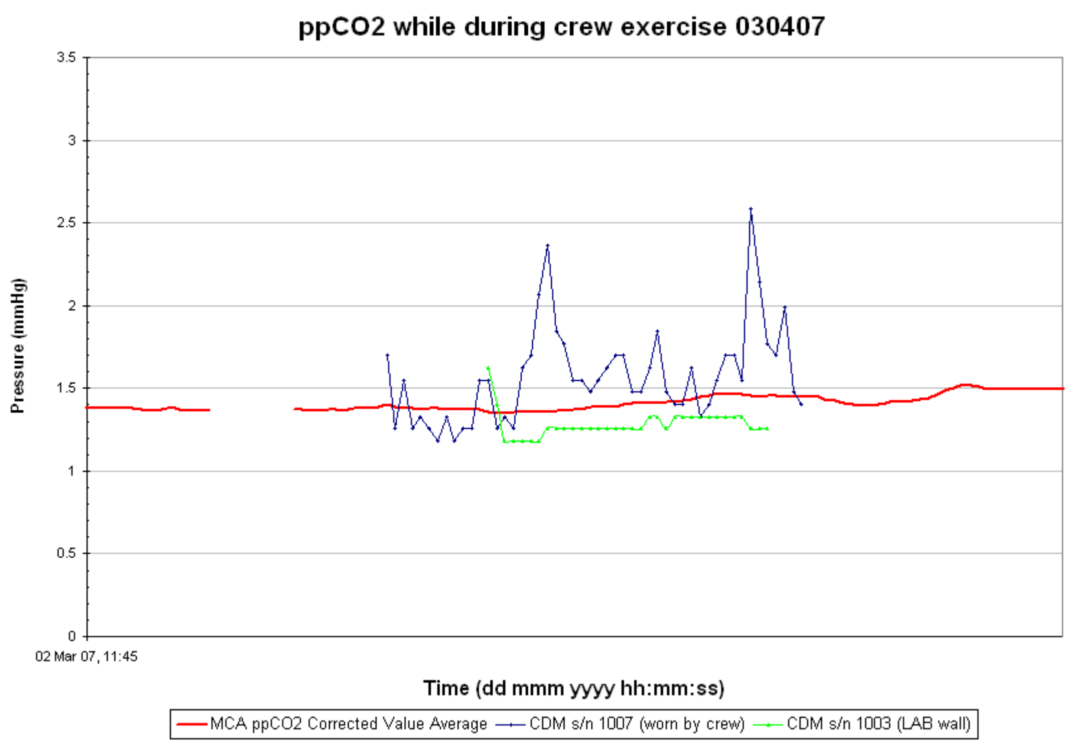


Figure 3. CO_2 concentrations during two-week periods centered on headache events (time interval outlined by dotted lines) reported in the Longitudinal Study of Astronaut Health and on Expeditions 12-15 and 17. Date is plotted on the horizontal axis, $ppCO_2$ (mm Hg) on the vertical axis.

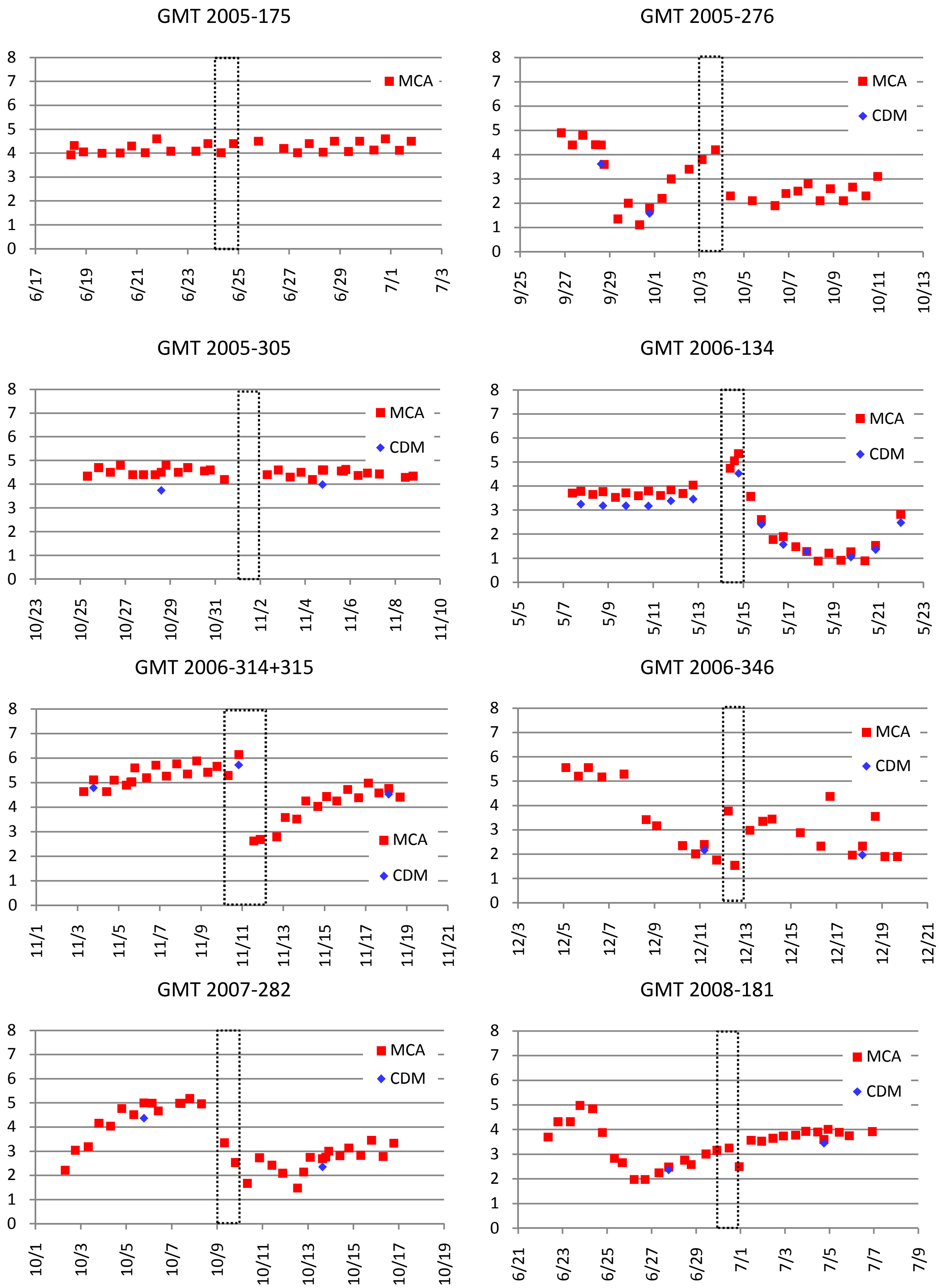


Figure 4. Distribution of $ppCO_2$ on days with and without reported headache. Headache occurrences were identified in the Longitudinal Study of Astronaut Health (LSAH) and Expeditions 12, 13, 14, 15, and 17. ("ExMC study")

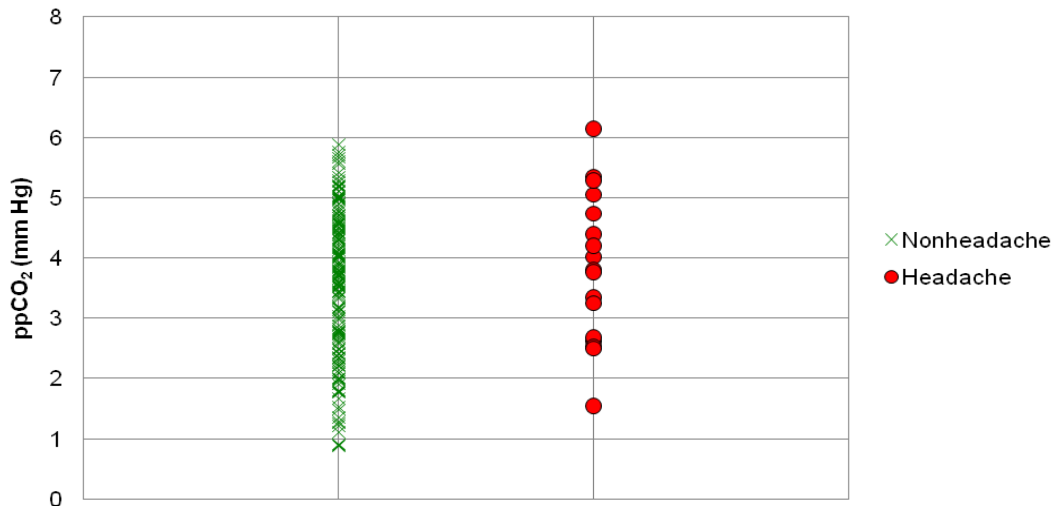


Figure 5. Comparison of $ppCO_2$ measurements taken by the Carbon Dioxide Monitors (CDM) and Major Constituent Analyzer (MCA) on board the ISS during periods of investigation for headaches in an ExMC study.

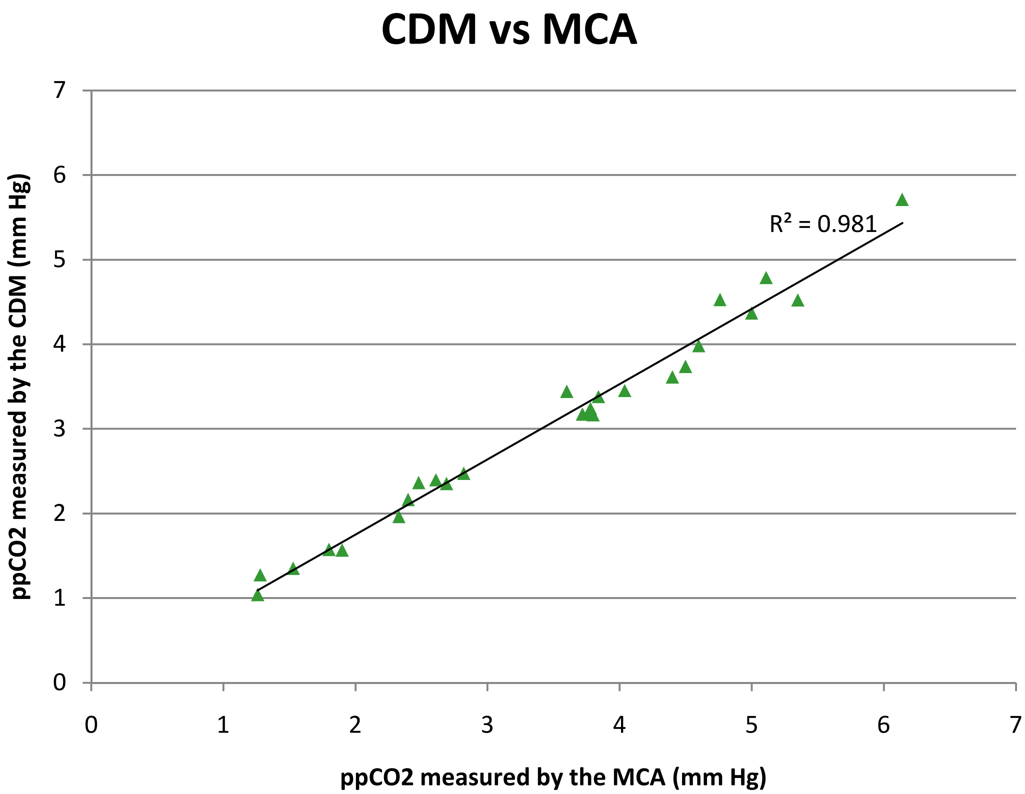
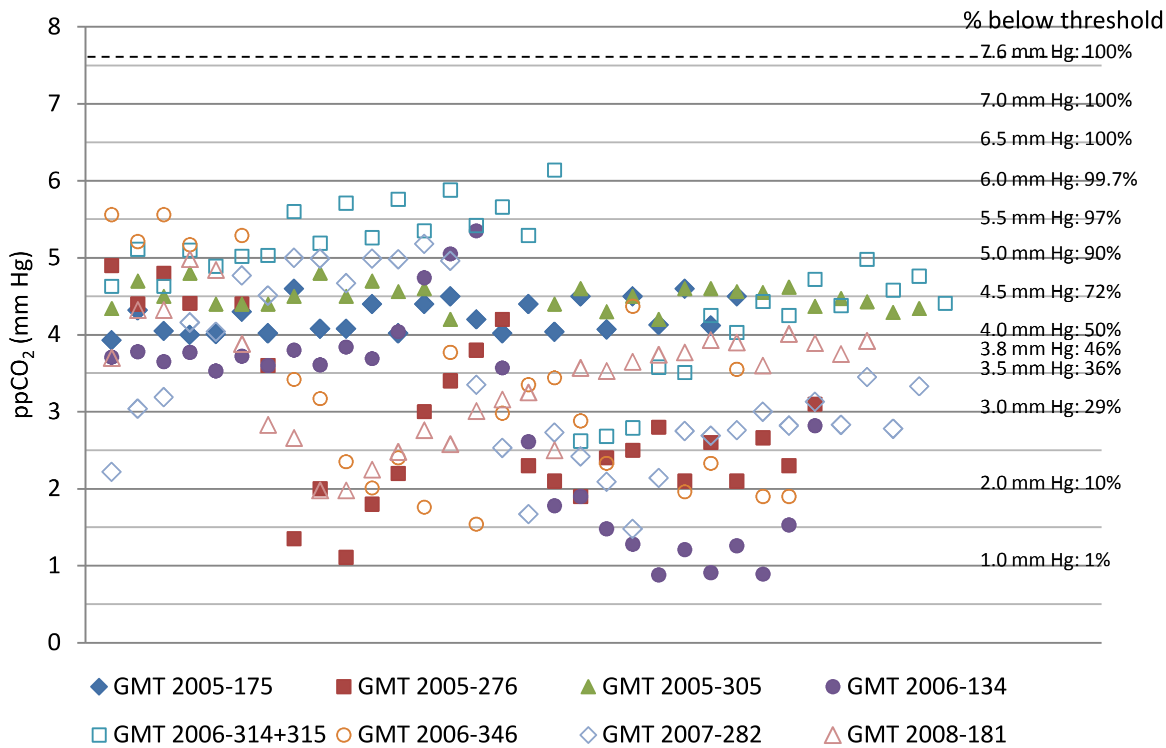
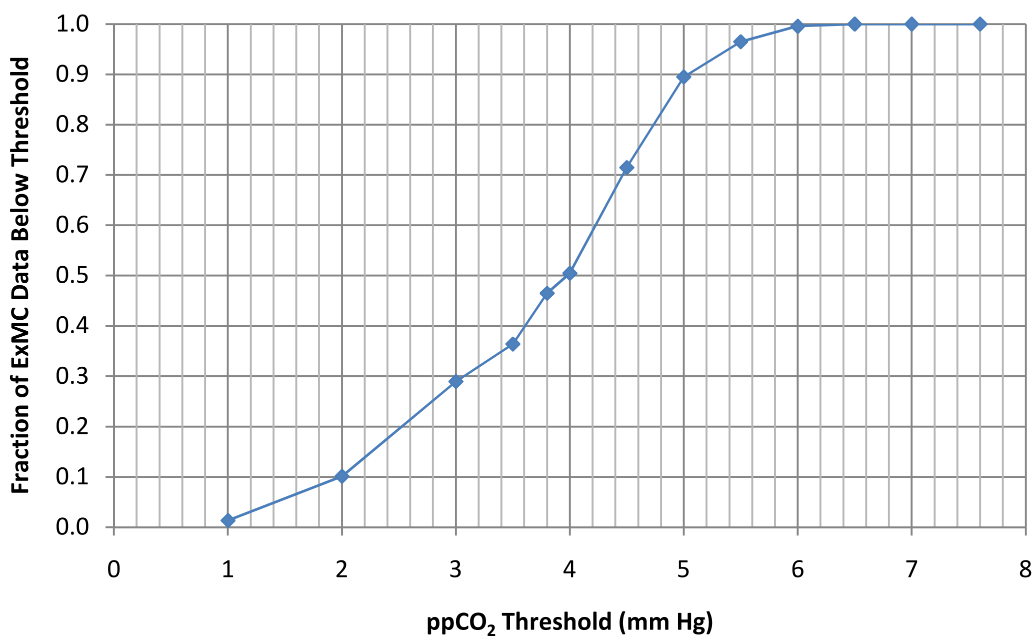


Figure 6. Threshold analysis of pooled ExMC study data (6A) **and fraction of CO_2 measurements that would fall below various $ppCO_2$ thresholds** (6B)**.** The current permissible exposure limit is 7.6 mm Hg.

(6A)



(6B)



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13. ABSTRACT *(Maximum 200 words)*

The effects of ambient carbon dioxide and exposure limits have been well studied on Earth. However, informal crew reports on the International Space Station have suggested that astronauts are developing CO2-related symptoms such as headache and lethargy at lower than expected CO2 levels and that symptoms tend to resolve when CO2 level is decreased. In-flight data to date support an association between elevated ppCO2 and CO2-related symptoms, but more research is needed to conclude causality. What appears to be increased CO2 sensitivity in microgravity may be attributable to individual predisposition to CO2 retention, adaptation to microgravity, and local fluctuations in CO2 that are not measured by fixed sensors. A review of the current occupational exposure limits supports lowering of the permissible exposure limit for the ISS and beyond, although evidence-based limits for space flight have yet to be defined.

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