REDUCED GRAVITY AND AEROSOL DEPOSITION IN THE HUMAN LUNG. Chantal Darquenne and G. Kim Prisk. Dept. of Medicine, University of California, San Diego, USA (9500 Gilman Dr., MC 0623A, La Jolla CA, 92093-0623, cdarquenne@ucsd.edu).

Introduction: The deposition of aerosol in the human lung occurs through a combination of inertial impaction, gravitational sedimentation and diffusion. For 0.5 to 5 μm-diameter particles and resting breathing conditions, the primary mechanism of deposition in the intrathoracic airways is sedimentation, and therefore the fate of these particles is markedly affected by gravity. Besides one experimental study performed in the 1970s [1], our laboratory has performed all of the experimental studies of aerosol deposition in the lung in altered gravity to date [2-12]. These studies have mostly been performed in humans during parabolic flights both in microgravity (μG) and hypergravity (~1.6G). This abstract provides an overview of those studies as a basis for the consideration of aerosol deposition in the reduced gravity of Mars.

Overall deposition: We first performed total deposition studies of 0.5-3 μm-diameter particles in normal gravity (1G), microgravity (μG) and hypergravity (~1.6G) using the NASA Microgravity Research Aircraft [2]. Subjects continuously breathed aerosol from a reservoir at a constant flow rate (~0.45 l/s) and breathing frequency (~15 breaths/min). Data showed that deposition increased with increasing G level. However, in μG, deposition of the small particles (~1μm) was higher than predicted by the numerical models. As inertia is negligible for these small particles and sedimentation is absent in μG, the higher deposition was explained by a larger deposition by enhanced diffusion resulting from previously unaccounted for mixing effects. While the overall change in total deposition caused by this process in 1G might be small, the effect may be disproportionately large if deposition occurs in the sensitive alveolar region of the lung, a region where the subsequent clearance of deposited particles is significantly slower than in the central airways [13].

Regional deposition: In order to probe the details of aerosol deposition, we undertook a series of bolus deposition (DE) and dispersion (H) studies in altered G levels [3-5]. A small bolus containing 0.5, 1.0 or 2.0 μm aerosol particles was introduced at predetermined points in an inspiration from residual volume to 1 liter above functional residual capacity. Penetration volumes (V_p) of the bolus ranged from 150 to 1500 ml, and in doing so directly probed deposition in the central airways (V_p= 150 ml), moving towards the periphery as penetration volume was increased. For each particle size, the data showed that, at shallow V_p (<200ml), DE and H were not different between gravity levels. In contrast, at larger V_p, when the aerosol bolus reached the alveolar regions of the lung, DE and H were strongly dependent on the G level. The steady increase in dispersion with increasing V_p suggests a continued presence of mixing processes in the early generations of the acinar region. This mixing may facilitate particles entering the alveolar cavities and eventually depositing.

Understanding "enhanced diffusion": We performed a series of bolus studies with a protocol designed to induce complex folding patterns within the lung [7]. Small flow reversals were imposed during a 10-sec breath-hold that followed the inspiration of 0.5 and 1 μm aerosol bolus. This protocol was based on the suggestion that irreversibility of alveolar flow combined with a stretched and folded pattern of streamlines can lead to a sudden increase in mixing and therefore deposition in the lung [14, 15]. Contrary to our expectations, the data showed that increasing the number of flow reversals had almost no effect on aerosol dispersion and deposition. We concluded that the mechanism of stretch and fold likely occurred during the one breathing cycle included in the basic maneuver. This conclusion is consistent with the complex mixing patterns observed by Tsuda et al. [14] in rat lungs after only one breathing cycle. This conclusion is important as it provides a mechanistic basis to explain what we previously described as "enhanced diffusion resulting from unaccounted mixing effects" that was found in our total deposition studies [2].

Retention of deposited particles in reduced gravity: The other important aspect of understanding aerosol effects in the lung is the residence time of the particles following deposition. Depending upon the lung region where particle deposit (airways versus alveolar region), these residence times differ by several orders of magnitude. The spatial distribution of coarse particles (MMAD ≈ 5 μm) deposited in the human lung was assessed using planar gamma scintigraphy [9]. Radiolabeled particles (Tc^{99m}) were inhaled in a controlled fashion (0.5 l/s, 15 breaths/min) during multiple periods of μG aboard the NASA Microgravity Research Aircraft and in 1G. In both cases, deposition scans were obtained immediately post inhalation and at 1h30 min, 4h, and 22h post inhalation. Relative distribution of deposition between the airways and the

alveolar region was derived from data acquired at the various time points. Data showed that the absence of gravity caused a smaller portion of 5 μm particles to deposit in the lung periphery than in the central region where deposition occurred mainly in the more central airways. This is consistent with the absence of gravitational sedimentation, which is normally dominant in the smaller peripheral airways.

Because this study utilized only coarse particles, the question of the site of deposition of fine particles (i.e., 0.5–2 μm-diameter particles) in a reduced gravity environment remained unanswered. While there are no human data available to date, some insight may be gained from recent data we obtained in animals [12]. Using postmortem magnetic resonance imaging techniques developed in our laboratory [16], we measured aerosol deposition in lungs of rats that were exposed to aerosolized 0.9-μm-diameter particles both in μG and 1G. Deposition in the lung periphery of these animals was similar between G levels, although overall deposition tended to be less in μG than in 1G, consistent with the results in humans [2]. This suggests that potential toxicological effects of aerosol exposure in a low gravity environment, such as the surface of the Moon or Mars, are likely not reduced compared with 1G. Because these data were obtained in rodents, one should be cautious in extrapolating these results to humans as there are major differences both in terms of airway tree structure and ventilation distribution between dependent and non-dependent regions of the human and rat lungs. However these are the only available data to date on the site of deposition of small particles in reduced gravity.

Implications for Mars exploration: While there is no doubt that the inhalation and deposition of small particles in the lungs is a health concern here on Earth, long-term spaceflight represents a situation in which aerosol deposition may also be an important health consideration. In a spacecraft environment such as the International Space Station (ISS) or a future Lunar or Martian habitat, the potential for significant airborne particle loads is high as the environment is closed and sedimentation is either absent (as on the ISS) or greatly reduced (as in the case of a Lunar or Martian habitat). Furthermore, Lunar and/or Martian habitats will likely operate at an absolute pressure significantly less than sea-level. Studies in 1G of aerosol bolus transport while breathing low-density gas (80:20 Heliox, ~about one third of sea level air density) showed a reduction in deposition in the upper respiratory tract and large airways, and an increase in deposition in the peripheral lung [17, 18]. The combination of reduced gravity and reduced gas density on aerosol deposition that was representative of a lunar habitat (~390 mm Hg, 32% O2, i.e. gas density of ~53% of that of sea level air) was investigated with the hypothesis that such combination would increase the deposition of aerosol particles in the peripheral lung in a synergistic manner [10]. Data showed that, while minimally affected by gas density, deposition was significantly less in reduced gravity than in 1G for both gases, with a larger portion of particles depositing in the lung periphery under lunar conditions than Earth conditions. Thus, our data strongly suggest that reduced gravity rather than reduced gas density is the major factor affecting deposition in the lungs of astronauts exposed to airborne particulates.

Conclusions: Studies of aerosol deposition in altered gravity have shown a significant effect of gravity on the amount and sites of aerosol deposition in the lung, which may affect subsequent clearance, and may significantly increase the toxicological impact of inhaled Lunar or Martian dust.

A significant gap in knowledge still exists regarding the spatial distribution of fine particulates in the human lung in reduced gravity even though studies in animals suggest a trend for a shift from central to peripheral deposition for these particles, the same particles known to have the greatest toxicological potential. Filling this gap would help establishing safe exposure levels to extraterrestrial dust. This may ultimately aid in mitigation strategies by developing appropriate crew systems against dust inhalation that are neither under-designed and unsafe, nor over-designed and costly.

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References: [1] Hoffman, R.A. and J. Billingham. (1975). *J. Appl. Physiol.*, *38*, 955-960. [2] Darquenne, C., et al. (1997). *J. Appl. Physiol.*, *83*, 2029-2036. [3] Darquenne, C., et al. (1998). *J. Appl. Physiol.*, *85*, 1252-1259. [4] Darquenne, C., et al. (1999). *J. Appl. Physiol.*, *86*, 1402-1409. [5] Darquenne, C., et al. (2000). *J. Appl. Physiol.*, *89*, 1787-1792. [6] Darquenne, C. and G.K. Prisk. (2004). *J. Appl. Physiol.*, *97* 2083-2089. [7] Darquenne, C. and G.K. Prisk. (2008). *Eur. J. Appl. Physiol.*, *103*, 687-695. [8] Darquenne, C., et al. (2013). *J. Appl. Physiol.*, *115*, 546-555. [9] Prisk, G.K., et al. (2013). *Acta Astronaut.*, *92*, 15-20. [10] Darquenne, C. and G.K. Prisk. (2013). *Aviat. Space Environ. Med.*, *84*, 190-195. [11] Darquenne, C. (2014). *J. Aerosol Med. Pulm. Drug Deliv.*, *27*, 170-177. [12] Darquenne, C., et al. (2014). *J. Appl. Physiol.*, *117*, 880-886. [13] Moller, W., et al.

(2004). *J. Appl. Physiol.*, *97*, 2200-2206. [14] Tsuda, A., et al. (2002). *Proc. Natl. Acad. Sci. U S A*, *99*, 10173-10178. [15] Butler, J.P. and A. Tsuda. (1997). *J. Appl. Physiol.*, *83*, 800-809. [16] Oakes, J.M., et al. (2013). *Ann Biomed Eng*, *41*, 967-978. [17] Peterson, J.B., et al. (2008). *J. Aerosol Med. Pulm. Drug Delivery*, *21*, 159-168. [18] Anderson, M., et al. (1990). *J. Aerosol Med.*, *3*, 209-216.