Summary of Symposium (DRAFT)

Space Toxicology: Human Health during Space Operations

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Abstract

Space Toxicology is a unique and targeted discipline for spaceflight, space habitation and occupation of celestial bodies including planets, moons and asteroids. Astronaut explorers face distinctive health challenges and limited resources for rescue and medical care during space operation. A central goal of space toxicology is to protect the health of the astronaut by assessing potential chemical exposures during spaceflight and setting safe limits that will protect the astronaut against chemical exposures, in a physiologically altered state. In order to maintain sustained occupation in space on the International Space Station (ISS), toxicological risks must be assessed and managed within the context of isolation continuous exposures, reuse of air and water, limited rescue options, and the need to use highly toxic compounds for propulsion. As we begin to explore other celestial bodies *in situ* toxicological risks, such as inhalation of reactive mineral dusts, must also be managed.

Keywords

Spaceflight Operations, Space Toxicology, Human Health, Pulmonary Toxicity, Exposure Limits

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The Space Toxicology: Human Health during Space Operations symposium was chaired by Dr. Noreen Khan-Mayberry & co-chaired by Dr. John T. James as a part of the American College of toxicology (ACT) annual meeting. The focus on this sub-discipline of toxicology was intended to introduce the greater toxicology community to the unique toxicological risks and human health issues inherent during human spaceflight operations. Space toxicology presents unique challenges due to the confined & enclosed microgravity (or reduced gravity) environments. The astronaut crewmembers experience physiological changes that compound the complexity in managing their exposures to chemical contaminants. This symposium gave (1) an introduction to the history of Space Toxicology; (2, 3) the processes for setting standards and guidelines for air and water exposure; (4) the process of risked based monitoring; and (5) NASA's research on pulmonary toxicity to lunar dusts.

A History of Space Toxicology (John T. James, Ph.D.)

The possibility of toxic exposures during spaceflight was a concern from the beginning of human spaceflight by the United States. As our experience grew, NASA recognized that unique air-quality standards were needed to establish boundaries on air pollution and that the sources of pollution were innumerable. Monitoring strategies were developed to meet the challenges of managing toxic events and control strategies were implemented to restrict the probability of accidental releases. Despite our best effort, toxic events still occur and from each of these we learn to improve our risk profile to better ensure a healthy and productive crew.

Sources of Toxicological Risk to Space Crews

The earliest toxicological risk that concerned space capsule builders was the possibility of excess off-gassing of materials that would pollute the capsule breathing atmosphere.[1] This was managed by rigorous testing of all materials to ensure that the air revitalization systems could remove pollutants to safe levels. There was also concern that highly-toxic propellants could contaminate the extravehicular-activity suits during space walks, and then contaminate the capsule atmosphere when the crewmember returned to the capsule. Obviously metabolic products, especially carbon dioxide, had to be adequately managed to prevent adverse effects.

As experience accumulated over the decades of spaceflight, new sources made themselves apparent. These included utility compounds such as lubricants, cleaning agents and hygiene products that can gradually pollute the atmosphere. Sudden and potentially dangerous releases that had to be controlled included leaks of toxic compounds from payload experiments (e.g. tissue fixatives), batteries with toxic volatile components such as thionyl chloride, and thermodegradation of polymeric materials (e.g. shorting of electronic components). As vehicles aged and systems failed more frequently, we recognized additional sources of air pollution such as volatile products of microbial action, pollution from systems leaks (e.g. ethylene glycol), and corrosion of metallic materials (e.g. cadmium plated components) that can produce harmful particulates. Increasing complexity of space vehicles, such as the International Space Station (ISS) and the broader range of experiments conducted aboard spacecraft has made the job of controlling air pollution a substantial undertaking. Some modules of the ISS are more than a decade old and at one point there were 13 astronauts working aboard the vehicle while the Space Shuttle was docked to it.

Historical Overview of Spacecraft Maximum Allowable Concentrations (SMACs)

NASA in cooperation with the National Academy of Sciences, and later the National Research Council, has set safe exposure limits for those compounds anticipated to be present in spacecraft atmospheres. The initial effort in 1964 was to set continuous-exposure limits for the Apollo vehicles that were going to the moon and back – a journey that could take up to 2 weeks. This was done for approximately 80 compounds five years before the first successful voyage to the lunar surface and back.[2] Even before the first successful lunar landing, missions of up to 1000 days were being anticipated and limits of 90 and 1000 days were set for about a

dozen compounds.[3] The grand vision of long missions encountered the reality of high cost, so the mission durations shrunk, and the limits were adjusted to shorter time periods. There was a need for limits for a variety of short-duration flights, and in 1976 limits were established for Space Shuttle flights.[4,5] After a decade of shuttle flights, NASA began to envision an earth-orbiting space station in which crews would remain for 6-months periods. In addition, real-time on board air quality analyzers were being developed. Thus it made sense to set long-term limits for this space station that reflected stays up to 6 months and also to set short-term limits indicative of our growing ability to detect and quantify products from accidental releases such as combustion events. In the 1990s SMACs were set for exposures from 1 hour to 180 days.[6] In the past few years the possibility of long-term missions to distant celestial bodies has reappeared, and in 2008 NASA set limits for many compounds for continuous exposures up to 1000 days.[7]

Modern SMACs (those set since 1992) consider the physiological changes induced by spaceflight.[8] For example, the SMAC for benzene is reduced three-fold because of the excess risk from space radiation which targets the blood-forming cells of the bone marrow just as benzene does. Cardiac arrhythmias have been documented during stressful times in space, so SMACs for compounds that sensitize the myocardium to arrhythmias are reduced by a factor of 5 to compensate for this spaceflight-induced risk. The space station can be noisy and temporary hearing loss is not unusual in returned astronauts, so the limits on ototoxic compounds are reduced accordingly. Astronauts also loose approximately 10% of their red-blood-cell mass in space, so hematotoxicants have reduced limits for spacecraft atmospheres.

Air Quality Monitoring – Going High Tech

Historically NASA has obtained air samples during missions and then analyzed those samples when they are returned to the earth.[9] This approach has the advantage that samples can be thoroughly analyzed by large, complex instruments in the laboratory; however, some compounds are lost to the container walls or sorbents and the results may not be available until months after the samples are acquired. This means that any investigation of the source of unexpected compounds found in the samples is severely hampered. We wanted to alleviate this handicap and eventually allow astronauts to manage air quality problems with on-board resources. Thus in the early 1990s NASA began to develop a suite of instruments that can quantify combustion products and a large group of trace compounds. Identifying precisely which combustion products will be the greatest threat to the crew is not simple because it depends on the composition of the material burned, the temperature of pyrolysis, and the availability of oxygen. We are currently targeting carbon monoxide, hydrogen cyanide, and acid gasses as the most likely to be harmful. In terms of trace contaminant quantification, NASA has flown a volatile organics analyzer for 8 years[10], and is working with partners to explore use of a FTIR spectrometer,[11] a gas chromatograph/mass spectrometer,[12] and a gas chromatograph/differential mobility spectrometer.[13]

Toxicological Events during Spaceflight

Transparent Events: Some atmospheric pollution events aboard spacecraft are transparent to the crew. For example, the air conditioner units in the Service Module of the ISS, and in the Core module of the old Mir space station, periodically leaked Freon 218 (perfluoropropane), which is virtually non-toxic. This volatile compound spreads throughout the station complex and is nearly impossible to scrub from the atmosphere. Formaldehyde is produced by off-gassing and at times has exceeded limits set to protect against mucosal irritation, although no such irritation has been reported. It is always more concentrated in the U.S. Laboratory module than in the SM.[14]

Minor Events: Toxicological events that are sufficient to elicit minor symptoms in the crew have occurred at least since the days of Apollo. Lunar dust, when floating in the spacecraft atmosphere caused the astronauts to don helmets until the dust was cleared. On rare occasions the astronauts reported respiratory symptoms from brief exposures to the dust. One ground-based worker seemed to develop increasing sensitivity to the dust when he worked with it on several occasions.[14] During the return voyage of the ill-fated Apollo 13 capsule from its swing around the moon, the ability to scrub CO2 was much diminished. The CO_2 levels eventually reached about 15 mmHg (2%), but no specific symptoms were ascribed to this exposure.[16] On occasion carbon dioxide accumulates in pockets that are poorly ventilated and this has caused minor discomfort and headaches. In space there is no such thing as “up” so convection does not move warm, carbon-dioxide-laden breath away from the face. In a stagnant area one can easily rebreathe his own exhaled breath repeatedly, causing minor symptoms. Canisters with LiOH have been used for many years to remove CO2 from the atmosphere; however, if the LiOH dust is not vacuumed from the canisters before they are inserted into the air revitalization system, astronauts can experience minor upper airway irritation.

Fires or pyrolysis events [heating to the point of breakdown of a polymer] are always a concern during spaceflight. In 1997 aboard the Mir Space Station the oxygen generator caught fire and was destroyed in an oxygen-rich blaze of rather spectacular proportions.[16] The event was obvious to the crew, so they donned protective masks and did everything they could to stop the fire and then clean up the atmosphere. Although this was a frightening event for many reasons, it was not a major toxicological event because the oxygen-rich fire produced very little CO. It did produce a few ppm of benzene, but this was rapidly scrubbed from the atmosphere by the Russian air revitalization system. Also, during the 1990s there were several minor events aboard the Space Shuttle involving pyrolysis of electronic components such as wire insulation, diodes, and resistors. These events produced a strong burned-electronic smell in the cabin and plenty of anxiety, but no serious toxic effects were reported.

Microbial contamination of spacecraft systems that are aqueous-based can occur under favorable conditions. Under some conditions this can result in significant air pollution. During the STS-55 mission in early 1993 the waste management system malfunctioned, so the crew began to place some waste in contingency bags. Periodically the bags’ contents had to be emptied (squeezed) through a port for disposal into space. The crew reported that noxious odors had contaminated the areas near the bags and that they were not inclined to continue the emptying process. An air sample was taken and its analysis showed three di-methyl sulphides compounds. Using bags identical to the ones on orbit and similar waste material, we

demonstrated microbial production of these compounds and penetration of them through the walls of the storage bags.[18]

Moderate Events: Fortunately such events have been unusual throughout the course of human spaceflight. The earliest event that caused moderate toxicological effects occurred aboard STS-40 in 1992.[18] On orbit it was noted that the refrigerator was emitting an acrid odor and excess offgassing was suspected. Crewmembers periodically went to a different module to get fresh air. Eventually, the unit was unpowered and all openings taped. When the unit was disassembled on the ground engineers discovered that the fan motor had overheated. This burned its housing, which was made of polyoxyethylene, an excellent source of formaldehyde when heated. The overheating was caused by set screws on the fan shaft couplers coming out against a guide sleeve so that the shaft could not turn. Since there was no thermal protection on the motor, power continued to be supplied to the locked motor, causing overheating. The odor was so strong that if the crew had not been able to get fresh air in another module, the flight may have been stopped early.

During the late 1990s aboard the Mir space station there were repeated leaks of the ethylene glycol heat-exchange fluid. The vapors caused mucosal irritation in the crewmembers and if they encountered a sizable bleb of the fluid in the face, then the eyes became extremely irritated. The leaks occurred primarily in the Kvant module where the highest concentrations remained. Once a leak occurred the fluid lodged on cooler, nearly-inaccessible surfaces and remained there almost indefinitely. Ethylene glycol also ended up in the water-recovery system where its removal was problematic.[19]

Another moderate pyrolysis event occurred in 1998 aboard Mir about one year after the spectacular oxygen-generator fire noted above.[20] At face value this seemed to be a much less significant event; however, toxicologically it was much more important. A hot filter had been prematurely switched into the trace-contaminant removal system and this caused a down-stream cellulose filter to burn. A small amount of smoke was observed; however, a few hours later, crewmembers experienced headaches and nausea. An experimental monitor for CO was aboard and was showing readings above 400 ppm; this was confirmed to be accurate by the amount of CO found in a grab sample that was analyzed on the ground much later. The levels of blood carboxy-hemoglobin were estimated from the airborne concentrations of CO. This was estimated to be as high as 40%, which explained the reported symptoms. The peak blood carboxy-hemoglobin concentration occurred approximately 5 hours after the burn. This explains why the symptoms were delayed. Although much less obvious than the oxygen generator fire this “small” fire was a toxicologically dangerous event.

In 2002, a moderate event occurred aboard the ISS when portable filters used during extravehicular activity were regenerated with heat to discharge pollutants from the filters into the ISS atmosphere.[21] These specific filters had been in a position to absorb ISS air pollutants for 6 months, so they were much dirtier than expected. A few hours into the regeneration process the crew reported noxious odors. The generation was stopped and the crew took refuge in another module (with hatch closed) until the air revitalization system clean the

pollutants discharged during the regeneration process. This required about 30 hours. Samples taken during this time showed high concentrations of 1-butanol and ethyl acetate.

Severe Event: Only one toxicological event can be classified as severe. In 1975 the United States and Russia did a demonstration project in which spacecraft from the two countries docked in space.[22] The Apollo capsule was used by NASA for the rendezvous. After undocking, as it was returning back through the atmosphere, the capsule interior was repressurizing through a pressure-relief valve by allowing outside air to enter. Unfortunately, the thrusters were still active because the capsule's descent was unstable. This caused nitrogen tetroxide fumes to enter the cabin and decompose into NO_2. The capsule concentrations peaked near 700 ppm (rough indirect estimate of NO_2). The crewmembers developed respiratory symptoms after recovery and were given chest X rays the next day. These showed patterns consistent with alveolar exudates. Corticosteroid treatment was given and the X rays were normal five days after landing. No long-term health effects were reported in this crew.

NASA has developed a set of air quality standards (SMACs) to define levels to which air pollutants must be controlled to protect crew health. Unfortunately, toxicological events are a normal part of human spaceflight. Reactive compounds useful as propellants can pose a risk to the crew. High-temperature components and many electronic devices invite pyrolysis of polymeric material such as wire insulation or components of circuits. Payloads and systems contain toxic compounds that can escape containment and evaporate into the air to expose crews. On board air monitors will facilitate our ability to manage these events when they occur; however, the first line of defense is to design out the possibility of a toxic exposure-an almost impossible task given weight and cost constraints of our incredibly complex spacecraft.

Spacecraft Maximum Allowable Concentrations – SMACs (Rochelle Tyl, Ph.D.)

History of SMACs

SMACs are defined as "the maximum concentrations of airborne substances that will not produce adverse health effects, cause significant discomfort, or degrade crew performance," although short-term SMACs are set for contingencies and allow for temporary, minor effects. NASA requested that the National Research Council (NRC) of the National Academies develop guidelines for establishing SMACs for various airborne contaminants and to review previous SMACs for various spacecraft contaminants to determine whether NASA's recommended exposure limits are consistent with the guidelines recommended by the Committee. The NRC developed criteria and methods for preparing SMACs published in its 1992 report. Since then, NRC's Committee on Spacecraft Exposure Guidelines has been reviewing NASA's documentation of chemical-specific SMACs in reports published in 1994, 1996, and 2000. The current report (NRC, 2008) is an update of 19 of the original SMACs by an Expert Panel convened by the NRC.

The determination of SMACs (and SWEGs) has become even more important now to maintain sustained occupation in space on the International Space Station (ISS). Toxicological risks must be assessed and managed within the context of isolation, continuous exposures, reuse of air and water (from condensation on ISS walls and equipment), limited rescue options, and the need to use highly toxic compounds for propulsion. In its present configuration, the ISS can carry a crew of 3-6 astronauts for up to 180 days. Several hundred chemical contaminants are found in its closed-loop atmosphere (most are at very low concentrations).

The present NRC Expert Panel objectives were to update the National Aeronautics and Space Administration (NASA) Spacecraft Water Exposure Guidelines (SWEGs) and Spacecraft Maximum Allowable Concentrations (SMACs) from the last evaluation in 1992, using the best available toxicologic risk assessment methods based on new studies, new data, new technologies, and new concerns.

Unique Population of Astronauts

Astronauts are still healthy, bright, dedicated, and educated, but new concerns are: (1) they are not all Caucasian (they are of different ethnicities with possible ethnic-specific susceptibilities and concerns); (2) they are not all men; and (3) they experience physiological adaptation to microgravity that can make them especially or uniquely sensitive to toxicants. The durations of space flight for which SWEGs and SMACs are to be assigned have been extended to 1,000 days for anticipated longer space flights (previously just to 180 days). The concerns are for astronaut performance in flight and for any adverse consequences from flight when they return. The SMAC classification scheme by duration and criteria is presented in Table 1.

Table 1. SMAC Classification

1 and 24 hours	Emergency situations, temporary discomfort (mild skin or eye irritation) may occur, but if the SMACs are not exceeded, there should be "no marked effect" on judgment, performance, or ability to respond to emergencies
7, 30, and 180 days	Continuous SMACs, guideline concentrations to prevent adverse health effects, either immediate or delayed (over the course of a lifetime), and to avoid impairing crew performance
1000 days	For longer space missions beyond low earth orbits and to other celestial bodies

Methods and Process for evaluation and setting of SMACs

The information evaluated by NASA and the NRC subcommittee to set SMACs includes (1) physical and chemical characteristics of contaminant (2) relevant *in vitro* toxicity studies; (3) toxicokinetic studies; (4) mechanistic studies; (5) animal toxicity studies conducted over a range

of exposure durations; (6) genotoxicity studies; (7) carcinogenicity bioassays - 2 years rat, 18 months mouse and (8) human clinical and epidemiology studies. The toxic effects of concern included (1) mortality (2) morbidity (3) functional impairment including mucosal irritation and CNS depression (4) specific organ system toxicities such as hepatic, renal, endocrine (5) neurotoxicity (6) immunotoxicity (7) reproductive toxicity (8) genotoxicity (9) carcinogenicity and (10) cardiotoxicity. The determinants evaluated were (1) identification of the most sensitive target organ or system affected (2) the nature of the effect on the target tissue (3) the exposure duration in relation to the SMAC being developed (4) the dose-response relationship for the target tissue, benchmark dose analysis may be applied (5) the rate of recovery (6) the nature and severity of the injury (7) Cumulative effects (8) toxicokinetic data (9) interactions with other chemicals and (10) the effects of microgravity.

The NRC expert subcommittee noted that toxicity data from human studies are most applicable and are used (when available) in preference to data from animal or *in vitro* studies. Toxicity data from animal species most representative of humans in terms of toxicodynamic and toxicokinetic properties are used for determining SMACs. Toxicity data from inhalation exposures are most useful for setting SMACs for airborne contaminants, because inhalation is the most likely route of exposure.

NASA toxicologists wrote a draft document for each chemical, identifying the key (driver) studies. The draft document and the key papers on which it is based were provided to the NAS committee. The committee members examined the document with special focus on concerns in their area(s) of expertise; additional papers were identified by committee members and distributed. The committee had conference calls and met in person to discuss each draft document, and provided questions, comments, additional edits, concerns, etc., to each author. The author of each document revised it according to the committee's comments, and the revised document was reviewed again at a subsequent meeting (with additional revisions if necessary). Once the document was accepted by the subcomittee, it was turned over to the NAS editorial staff for preparation for publication.

Ethanol

Existing literature focused on health consequences of oral consumption and abuse of alcohol. There was a lack of information on inhalation exposures. Ethanol is a significant additive or replacement for motor vehicle fuels to limit CO and ozone. Previous toxicological endpoints were neurotoxicity irritation, hepatotoxicity, and flushing. New concerns for the ISS are that ethanol is present in water condensates (as high as 156 mg/L), with a mean 50-55 mg/L, higher in U.S. laboratory than in Russian Service Module, and Russian processing equipment is affected by ethanol (and other volatiles). In addition, there is a need for 1,000-day SMACs[23].

Propylene Glycol

On the Soviet Mir Space Station, ethylene glycol (EG) was used as a coolant. An incident occurred where several gallons leaked out and EG was detected in the air (as vapor) and in the humidity condensate to be used for drinking water. Given the toxicity of EG (CNS, renal, reproductive, developmental, etc.), NASA proposed PG for use as a coolant for the Orion crew

exploration vehicle to the moon, Mars, and other solar system destinations[24]. Therefore, we reviewed the inhalation toxicology literature on PG to set SMACs for 1 hour through 1000 days to PG vapors. There were no reports of human toxicity or deaths from exposure to PG vapors; there are clinical reports of PG-associated toxicities: hyperlactatemia, metabolic acidosis, hyperosmolarity, renal toxicity. No human data on short-term, subchronic, or chronic PG exposures, no human data on PG-induced carcinogenicity, no data on genotoxicity in humans/animals by inhalation of PG vapors and no standards or health values for PG exist.

The American Industrial Hygiene Association (AIHA) established an 8-hr, time-weighted average exposure level (50 ppm for vapor). The Agency for Toxic Substances and Disease Registry (ATSDR) did not derive an acute inhalation minimal risk level but did derive an intermediate duration of 0.009 ppm (based on nasal hemorrhaging in rats). There is one nose-only subchronic study in SD rats on inhalation of PG vapors[25], which is the basis for all SMACs longer than one hour.

A total of 19 airborne contaminant chemicals and classes were evaluated or re-evaluated by this Expert Panel[26].

Risk-Based Monitoring of Spacecraft Pollutants (Noreen Khan-Mayberry, Ph.D.)

As air and water quality standards became available specifically for human spaceflight, the need to perform real-time, onboard monitoring of some of the riskiest compounds became evident[27]. NASA has developed and used various instruments to monitor selected combustion products since the early 1990s. We have targeted other pollutants for monitoring including carbon dioxide, propellants, and formaldehyde. NASA has also developed broad-spectrum trace organic analyzers for air quality monitoring aboard the International Space Station. In addition, a total organic carbon analyzer has been flown to monitor water quality as we begin to recover water from urine.

NASA's knowledge of the compounds present aboard spacecraft gives Toxicologist the ability to calculate and predict which of these chemicals might become a toxic hazard[28]. Currently, NASA uses a variety of chemical monitors to manage predictable risks of air toxicants in the ISS or Shuttle.

Predictable vs. Non-Predictable

Toxicological risks in space environments are classified as predictable, known chemicals in spacecraft, and unpredictable, the off-nominal toxic release of chemicals[29]. Regarding predictable risks, Space Toxicologists have the benefit of knowing the chemicals that are on board spacecraft and can make predictions of which chemicals may become toxic. There are a substantial number of particulate and volatile space contaminants that have been identified and quantified by NASA's space toxicology laboratory. Chemicals that are of greatest concern for assessing potential toxicity are those that target organs or organ systems that are already compromised by spaceflight induced physiological changes. The primary sources of

contaminants come from crew member metabolism and vehicular materials off-gassing. Unpredictable risks require a special approach from Space Toxicology. In order to detect and deal with off-nominal toxic releases, toxicology has put a suite of real-time monitors and medical support in place.

Response to toxic release is handled through medical and ECLS flight rules Vehicle propellants are monitored using a gold-salt method in the vehicle's air lock, which is an isolated compartment which astronauts use to ingress/egress from the vehicle[20,27]. By monitoring in the airlock we can identify whether or not propellant material has contaminated the extravehicular activity (EVA) suits and is brought back into the vehicle[30]. If propellants are detected, NASA's flight rules define required procedural steps for removing propellants. Ammonia, which is used a vehicle coolant and is quite prevalent throughout the spacecraft, yet its escape is unlikely due to several barriers in place. However, if this highly toxic chemical were to migrate from the external thermal loops into the cabin, it can be monitored in ISS. If ammonia were detected, NASA flight rules will state the mandatory procedures which are based on the detection levels identified by the ammonia monitor.

Space Toxicologist – Health support of Human Spaceflight

Medical Support provided by the Space toxicologist includes assessing chemicals that will be brought into the space environment for potential toxicity prior to approval for spaceflight use. The Space Toxicologist also provides 24 hour per day, 7 days per week on call support. The toxicology website can be accessed to get further information on SMACs & hardware. The hazardous agent toxicology assessment process was initially created after STS-26 and implemented on a subsequent flight for the shuttle program. The ISS Hazardous Materials Summary Table (HMST) process was initiated based on the shuttle experience and was primarily payload based.

The primary assumption for training the crew about Hazardous Materials is that during spaceflight crew will be responding in an emergency situation using labels on the hardware and the HMST prepared by Space Toxicology is provided as a "medical dictionary" for crew reference. The official program requirement for HMST is documented in the Medical Operations Requirement Document. The Hazardous Materials database is available to crew, flight surgeon, many others necessary flight support personnel. The HMST database contains the locations, identities, and hazard ratings of "all" compounds (fluids, gases, and dusts) aboard the ISS and Shuttle.

Hazard classification depends on the inherent toxicity and amount of compound that could escape containment, assessing the containability if a chemical compound is released into the air and predicting the volume of dispersion after release[29].

Toxic Hazard Classification

Toxic hazards levels (THL) in space are classified according to the following criteria[29]. A "Non Hazardous" is rated 0, which indicates that a chemical has no more than mild, transient effects. A "Critical" hazard is rated 1 for chemicals causing moderate, lasting, but not permanent effects. Catastrophic hazards are rated 2-4 contingent upon their severity and the ability for the crew to isolate and remove the chemical contaminant. A "Catastrophic" hazard level 2 is assigned to a chemical that may cause severe, permanent contact effects and is containable, can be cleaned and isolated by crew. The THL 2 chemical must be either a solid or non-volatile liquid which has no systemic effects and causes moderate to severe irritation that has the potential for long-term performance decrement and will require therapy. A "Catastrophic" hazard level 3 is delegated to any chemical that may cause severe systemic effects and is containable. The THL 3 chemical must be either a solid or non-volatile liquid that would cause appreciable effects on perception, coordination, memory or the potential for long-term (delayed) critical injury (cancer) or may result in internal tissue damage. Irritancy alone does not constitute a level 3 hazard. A "Catastrophic" hazard level 4 is designated for any chemical that may cause severe contact or systemic effects and is not containable. The THL 4 chemical must be a gas, volatile liquid or fumes and has the potential for long-term decrement of crew performance, would cause appreciable effects on perception, coordination, memory or the potential for long-term (delayed) critical injury (cancer) or may result in internal tissue damage.

When assessing a chemical mixture a T-Values is calculated. The T-Value concept is calculated as follows:

$$T = C_1/SMAC_1 + C_2/SMAC_2 + \ldots C_n/SMAC_n$$

Where the C's are measured concentrations and SMAC values used in the calculation are those appropriate to the exposure time of the crew. T values can be sorted by toxicological group if necessary: irritants (aldehydes), Neurotoxicants (alcohols), Cardiotoxicants (chloro-fluoro carbons). The crew's breathable air is deemed safe if all group calculate to T values of < 1.

Toxic Chemical Identification Toxicity Labels in Space

All US hardware/payloads identified for toxicants prior to flight must contain a label so that the crewmembers and ground personnel can easily identify if the payload contains any toxic hazards (See Figure 1).

Figure 1. Toxicity Labels used on ISS & Shuttle Orbiter

All crews are briefed prior to flight so that they can identify toxic hazard labeling and to educate them of areas containing known toxic hazards. An example of a typical Crew Pre-Flight briefing of toxic hazards

includes a chart (see Table 2) that outlines the apparatus on board the vehicle or space habitat, the chemicals of concern and the expected toxic effects if a crewmember is exposed. The chart can also be used to clarify some myths about chemical exposures, such as Freon 218.

Table 2. Crew Pre-Flight briefing of Toxic Hazards

Apparatus	Chemicals	Toxic Effects
Elektron	1.5 L 26% KOH Pyrolysis products	*Ocular, Dermal* Corrosive to eyes and skin Odor only unless severe (THL 2)
Urine Pretreatment solution/treated urine	5L of CrO_3 and sulfuric acid solution/treated urine has pH of 1.5	*Ocular, Dermal* Irritation and permanent damage to eyes; skin irritation (THL 2)
Metox Canisters	Many if Regeneration is delayed	*Olfactory (Effluvium/Odor)* Noxious to intolerable odor (THL 1)
LiOH canisters	LiOH dust	*Ocular* Eye irritation, possibly severe (THL 2)
FGB batteries Battery Charger Mod Leaking battery	40% KOH electrolyte Thionyl chloride Caustic liquids	*Ocular, Dermal, Respiratory* Severe injury to eyes/ skin (THL 2) Respiratory injury (THL 4) Severe injury to eyes/skin (THL 2)
SM Air Conditioner	Freon 218	No adverse effects (THL 0)
WAICO	fixatives	*Ocular* Lasting injury to eyes (THL 2)

Space Toxicology Monitors

NASA has developed and used various instruments to monitor selected combustion products since the early 1990s as well as instruments for selected high risk pollutants including carbon dioxide, propellants (hydrazine, MMH, UDMH), and formaldehyde. NASA has also generated broad-spectrum trace organic analyzers (VOA, GC-DMS) for monitoring air quality aboard the International Space Station. To ensure the condition of water recovered from urine, a total organic carbon analyzer (TOCA) is utilized on ISS to examine water quality. These instruments provide real-time and archival (returned to Earth for analysis post-mission) monitoring of chemical contaminants.

Figure 2. Grab Sample Container (GSC)
from L to R: Original model, New Model

Archival instruments are returned to the toxicology lab post-mission for analysis. Grab Sample Canisters are used to monitor air quality at the crew's first-entry into a space vehicle/habitat as well as during nominal scheduled times and contingency samples for use during off-nominal events. The GSC has 3 surrogate standards, the sample is aspirated by vacuum in <5 seconds and is analyzed in the laboratory by GC and GC/MS. Limitation of the GSC are that reactive compounds are lost. The old model (see Figure 2) had a problem-valve that may not be sealed well after sampling. The new model (see Figure 2) eliminated the valve problem and takes up less space allowing for more samples to be taken.

Figure 3. Formaldehyde Badge (FMK)

Formaldehyde Badges (see Figure 3) are used for nominal sampling, these low cost ($20 USD) peel and stick badges can be used to detect formaldehyde in an area or stuck to a crew member to detect personal exposures. Formaldehyde is trapped in badge matrix by diffusion. The typical sample time is 24 h (in pairs). During laboratory analysis formaldehyde is eluted from badge and analyzed by spectrophotometry. The badges limitation is that it must have sufficient face velocity of air flow.

Real-time monitors give the crew and ground personnel access to real time chemical constituents in air; some are broad spectrum, while others target specific components. The Compound Specific Analyzer for Combustion Products (CSA-CP) is a continuous monitor that uses electrochemical sensors to detect CO, HCN, HCl, and O_2 (see Figure 4)[31]. The Carbon Dioxide Monitor (CDM) is a special-purpose infrared spectrometer for the detection of CO_2 (see Figure 5) it has a 6% upper detection limit and an 18 hour battery life. The sample is pumped into the CDM which contains a water and particle filter and uses infrared absorption of measure CO_2 [32]. The Volatile Organics Analyzer (VOA) quantifies compounds by using a dual gas chromatograph/ion mobility spectrometer (see Figure 6). The VOA takes

Figure 4. Compound Specific Analyzer for Combustion Products (CSA-CP)

Figure 5. Carbon Dioxide Monitor (CDM)

and in situ sample or remote sample by bag; it was used by NASA many years past its life expectancy, is also very large and has a small dynamic range and no "unknown" chemical library. The GC-DMS Gas Chromatography/Differential Mobility Spectrometry microanalyzer VOA is the next generation replacement of the VOA for detection & quantification of select volatile organic compounds; it is much smaller (see Figure 7). The Total Organic Carbon Analyzer (TOCA) measures conductivity, pH, total carbon, and total inorganic carbon (see Figure 8). Key parameter is the TOC. The TOCA uses small amount of hazardous reagents and TOC measurements confounded by addition of formate to some make-up water[33]. The replacement TOCA or TOCA 2 (see Figure 9) does not require the crew to add hazardous reagents and allows real time screening of organic content in consumable potable water. Archival analysis of water is done via water sampling bag (see Figure 10). This device has been used to detect highly toxic chemicals such as Cd, the source of which was traced back to a Cd spring.

Figure 6. Volatile Organics Analyzer

Figure 7. Gas Chromatography/ Differential Mobility Spectrometry (GC-DMS)

Figure 8. Total Organic Carbon Analyzer (TOCA)

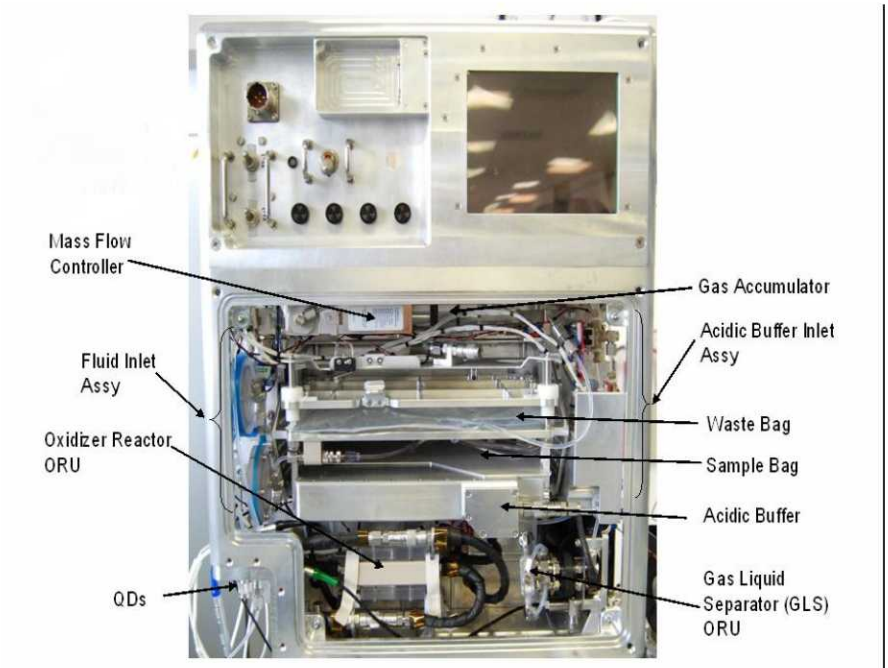

Figure 9. Next generation Total Organic Carbon Analyzer (TOCA 2)

Figure 10. Water Sample Bag – Archival analysis

Conclusion

Spaceflight risk assessment involves controlling predictable risks and managing unpredictable risks with a suite of monitoring devices. Toxic hazard assessments depend on a chemical's inherent toxicity, the releasable amount, volume of dispersion, and containability after release. On orbit analytical instruments must be small, reliable and use minimal resources and trace-contaminant toxicity must be considered as a sum at the target organ level. Reclaimed water must be analyzed for airborne toxicants. As we move out of low earth orbit and explore other celestial bodies space toxicology risk assessment will include hazards from reactive, *in situ* dust and effective on-site monitoring[34].

Pulmonary Toxicity of Lunar Dust (Chiu-wing Lam, Ph.D.)

As NASA plans to visit various planets and celestial bodies in our solar system, the concern of exposing space explorers to various types of ultrafine dusts, such as the highly reactive lunar dust is considered to be a real concern. If NASA returns to the moon one plan outlines building an outpost on the lunar surface for long-duration human habitation and research. The Shackleton Crater area of the lunar south pole is the landing site of choice (see Figure 11). The crater lies entirely within the rim of the immense Aitken basin (~1500 miles in diameter), which is the largest and oldest impact basin on the Moon. This basin is roughly 8 miles deep, and an exploration of its properties could provide useful information about the lunar interior[35]. The crater rim is illuminated by sunlight almost continuously; besides being subjected to smaller extreme temperature fluctuations than those that occur at the Apollo landing sites, the crater rim provides good access to solar energy. The interior of the crater is perpetually dark and very cold; any water that landed on the crater from cometary impacts would lie permanently frozen on or below the surface. An engineers' concept of a full lunar outpost is shown in Figure 12[36].

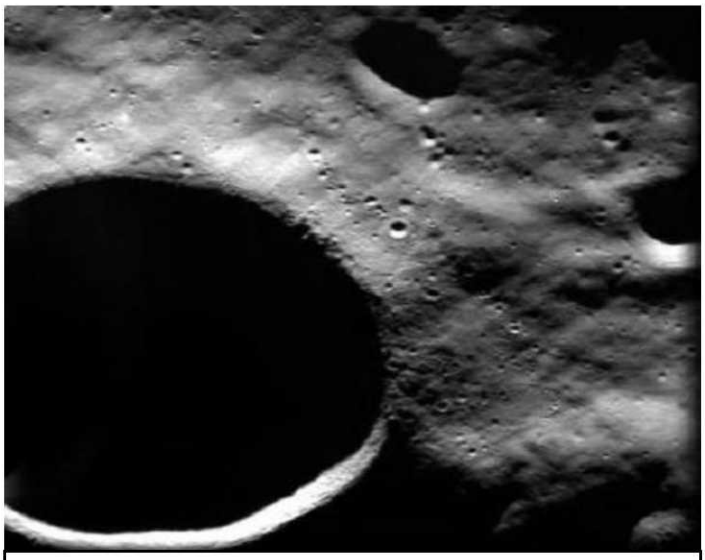

Fig. 11. Shackleton Crater at the lunar south pole, the site of choice for building a habitat.

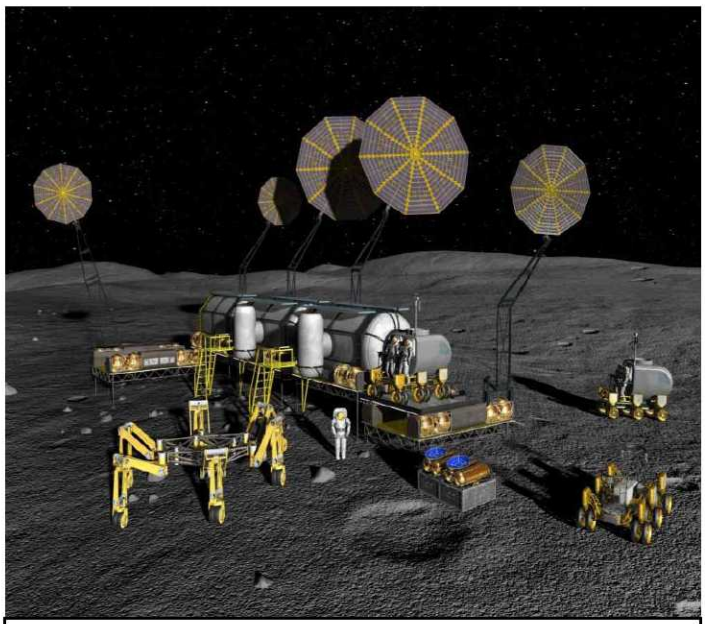

Figure 12. Engineers' concept of full lunar outpost

Besides having occasionally been hit by large comets, the surface of the Moon has consistently been bombarded by micrometeoroids for more than 4 billion years. During the high-speed impacts of these micro-grain interplanetary dusts, typically 0.05 mm in diameter, the force and heat melt, partially vaporize, and/or crush particles of surface regolith. Cooling welds the particles together into glassy and jagged-edged agglutinates, which are pulverized to fine dusts upon subsequent impacts. In the course of lunar history, these meteoritic

activities have created a relatively even particle-size distribution of the regolith over the whole lunar surface. The regolith contains about 10% to 20% fine dust with particle diameters less than 20 μm[37]. The lunar regolith resides in a near-vacuum environment and is constantly subjected to irradiation from solar ultraviolet light and x-rays in the daytime and solar wind at night; these solar radiations alternately impart positive and negative charges to the regolith. The surfaces of the charged lunar fine dust are expected to be populated with "unsatisfied" chemical bonds, making them very reactive[38,39]. While astronauts are living on the Moon, as they go in and out of the habitat (including bringing instruments, hardware, and spacesuits in for servicing or refurbishing) they will bring dust, which is very adherent, into the living quarters of the lunar outpost. The potential for dust contamination of the lunar habitat can easily be inferred and visualized by examining Apollo 17 astronaut Jack Schmitt's soiled suit (see Figure 13) and reading the Apollo crews' comments about exposure to lunar dust in the Command Modules during their return journeys to the Earth. Respiratory tract irritation resulted from lunar dust exposure was reported by crewmembers of Apollo 12, 16, and 17 missions[40].

Apollo 17 astronaut Dr. Jack Schmitt shows it was contaminated with fine lunar dust.

The lunar regolith is made up of minerals derived from anorthositic, gabbroic, and basaltic rocks that are also common in the Earth's crust; aluminosilicate and ferromagnesian silicate minerals including plagioclase feldspar, pyroxenes, and olivine make up the bulk of the lunar regolith[38] . According to Dr. Lawrence Taylor, a member of the NASA Lunar Geology Team, the samples of lunar surface soil collected during the Apollo program show that the regolith contains about 1% to 2% very fine dust (≤ 3 μm), which is respirable by humans; about 80% of the mineral in the fine-dust portion of lunar regolith is silica-rich glass[41]. The Solar activities and micrometeoroid bombardments make the very fine surface dust potentially reactive. Fine reactive dust in the habitat can be expected to produce toxicity in the lung if it is inhaled and could pose a health risk to astronauts living on the Moon. NASA has established a Lunar Airborne Dust Toxicity Assessment Group (LADTAG), which includes national experts in toxicology and lunar geology, to evaluate the risk of exposure to the airborne dust and to establish safe exposure limits for astronauts working in the lunar habitat; NASA has also directed its toxicology laboratory at the Johnson Space Center (JSC) to investigate the pulmonary toxicity of lunar dust in experimental animals to obtain the needed data. The NASA JSC Toxicology Laboratory has invited

National Institute for Occupational Safety and Health and other academic institutes to participate in these important toxicity studies.

General Design of Experiments

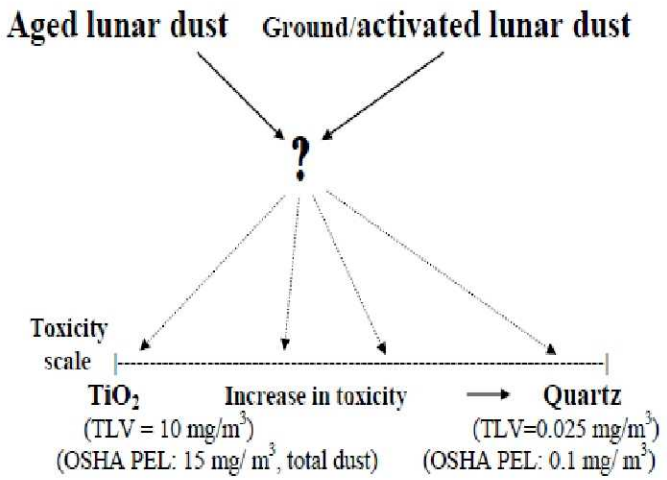

Figure 14. Comparative pulmonary toxicity study of lunar dust with reference dusts in rats by intratracheal instillation.

Assessment of the pulmonary toxicity of a dust is generally done first in rodents by an intratracheal or intrapharyngeal instillation (ITI/IPI) study, in which the dust of interest can be compared with reference dusts of known toxicity[42]. The ITI/IPI study is then followed by an inhalation study. Lunar dust samples in our (ITI/IPI) study will be tested simultaneously with two common reference dusts, titanium dioxide (Retile R-100, Du Pont) and crystalline silica (quartz or Min-U-Sil 5, U.S. Silica). The pulmonary toxicities of these two reference dusts are well characterized: titanium dioxide is low in toxicity while quartz is a fibrogenic dust that can produce a spectrum of lung lesions. The Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have set occupational exposure limits (permissible exposure limit [PEL] and threshold limit value [TLV], respectively) on both dusts. The comparative toxicities of the test dusts in these instillation studies will be useful for LADTAG to establish limits for astronaut exposure to the lunar dust (see Figure 14).

As discussed above, the dust particles on the lunar surface are subjected to cometary impact and are expected to remain chemically reactive in the high-vacuum lunar environment[38,39]. The lunar soil samples collected during the Apollo missions were exposed to air and moisture on their journeys to Earth, and exposed to trace levels of oxygen and water molecules during their prolonged storage on Earth. The NASA Geology Team believes that the Apollo lunar dust has been "chemically passivated" by these atmospheric components [34,43]. When freshly ground Earth minerals of the types found on the lunar surface (olivine, augite, and labradorite) were exposed to water, hydrogen peroxide was formed in concentrations raging from 0.9 to 25 nmol/m^2 mineral[44]. The NASA Geology Team believes that grinding will "restore" the chemical reactivity of the passivated lunar dust. They will isolate respirable fractions (diameter < 2 μm) of ground and unground lunar dust samples and provide them to the JSC Toxicology Group for evaluation of their pulmonary toxicity.

Intratracheal/Intrapharyngeal Instillation

The ITI/IPI on lunar dust will be carried out in mice and rats. The bronchioalveolar lavage fluids (BALF) will be obtained from rodents 7 and 30 days after the dust instillation to assess pulmonary inflammation and damage; variables to be assessed include lactate dehydrogenase activity, total protein and inflammatory cytokine concentrations, total cell counts, and cell differential. Lung histopathology will be microscopically evaluated in rodents 1 and 3 months after the dust instillation (see Figure 15). The lungs and lymph nodes will be examined for the presence of inflammation, necrosis, fibrosis, and other lesions.

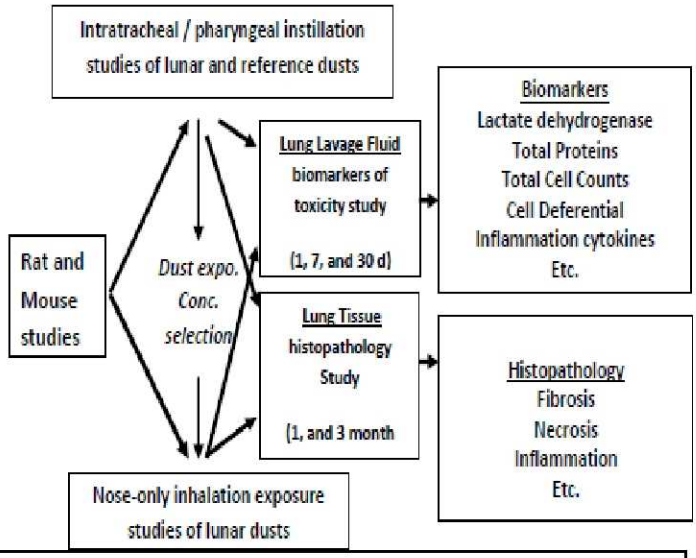

Figure 15. Outline of toxicity studies with lunar dusts in rodents.

Nose-Only Inhalation Studies

Figure 16. Nose-only inhalation exposure chamber systems, each equipped with a Vilnius Dry Aerosol Generator and a cyclone.

The data from these ITI/IPI studies could also be useful for determining the exposure concentrations for the inhalation toxicity study with lunar dust. From the ITI/IPI toxicity data, we could choose three exposure concentrations that would be likely to produce moderate, mild, and no effects in the lungs of exposed rats. Because of the limited quantity of lunar dust, the inhalation exposure will be carried out in nose-only exposure chambers. We are planning to carry out a 4-week inhalation exposure study. Battelle Northwest Group (Seattle, WA), after testing a Vilnius Dry Aerosol Generator (VAG), concluded that "aerosolization of small quantities of dry powders with VAG is controllable, consistent, repeatable and predictable." We set up two dust generation-

exposure systems (see Figure 16), each consisting of a VAG, a cyclone, and an NYU-Jaeger nose-only inhalation exposure chamber (CH Technologies, Westwood, NJ) like the one tested by Battelle. We tested the performance of our two exposure systems using a simulated lunar dust (JSC-1Avf, a fine dust sample isolated from a volcanic ash and provided by Dr. James Carter of the University of Texas at Dallas, Dallas, TX). The concentration profile of dust in each chamber was monitored by a Cassella Microdust Pro Real-time Dust Analyzer (Casella USA, Amherst, NH); the dust in a known volume of chamber atmosphere was collected (1 L/min) continuously for 5 hours on filter paper for quantitative determination of the average dust concentration in the chamber. The aerodynamic diameter of the dust particles was determined by an Aerodynamic Particle Sizer Spectrometer 3321 (TSI Incorporated, Shoreview, MN). Since the TSI 3321 could not give a mass median aerodynamic diameter (MMAD) of our test dust directly, the MMAD was estimated. We have acquired a Quartz Crystal Microbalance (QCM) Cascade Impactor Real-Time Air Particle Analyzer (California Measurements, Inc., Sierra Madre, CA) that could be used to obtain real-time chamber concentration and aerodynamic particle size information. After further refining our exposure systems and acquiring another nose-only chamber for exposure of control animals, we will carry out a pilot study with rats exposed to the lunar dust simulant. A study with real lunar dust will then be carried out in rats exposed for 4 weeks (5 h/d, 5 d/wk). BALF will be obtained from the rats after 7 and 30 days, while lung tissues will be harvested 1 and 3 months after the exposure for pulmonary toxicity assessment.

Results and Conclusion

We have conducted two intrapharyngeal instillation studies in C57/BL mice and have examined the toxicological parameters in BALF and histopathology lesions in lungs and lymph nodes. The data analyses have not been completed and will be presented at a later date. We tested the performance of our two nose-only inhalation exposure chamber systems, each equipped with a VAG and a cyclone, by conducting five 5-h runs on each system. Figure 17 shows the results of five 5-h runs in one of the chambers with lunar dust simulant JSC-1Avf, and Figure 18 shows the concentration profile of one 5-h

Run	Target	Casella	SD	Filter
1	75	77	10	31.1
2	75	79.9	9.9	29.2
3	75	81.6	16.6	27.5
4	75	76.6	11.7	29.3
5	75	77.1	13.8	29.3
Ave.		78.4		29.3

Figure 17. Chamber dust concentration profiles of five 5-hour-exposure runs without animals.

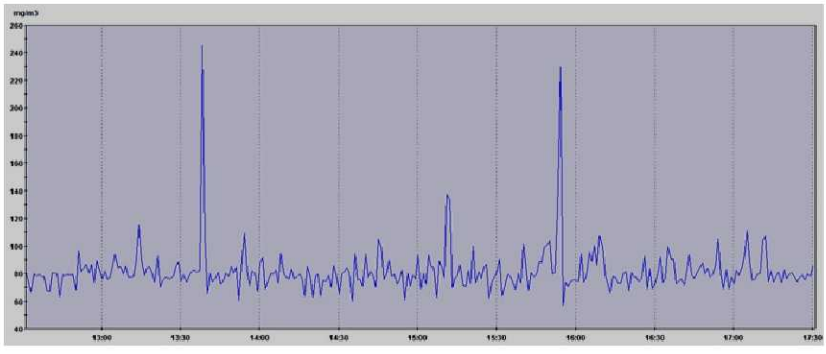

Figure 18. A typical chamber concentration profile of a 5-hour run (concentration recorded by Casella Microdust Pro Analyzer).

run recorded using the Casella dust monitor. The analytical results from the TSI 3321 allow us to roughly estimate the MMAD to be 2.8 μm and the geometric standard deviation of the dust in the chamber to be 1.5. From the results of the five 5-hour dry runs in each chamber system, we concluded that these systems are suitable for our lunar dust exposure. After further refinement and a successful pilot rat study with lunar dust simulant, we will conduct an inhalation study with lunar dust in rats. The results of both the ITI and inhalation studies will provide toxicity data needed to assess the health risk of dust exposures on the Moon and data for LADTAG to set safe exposure limits of lunar dust.

CONCLUSION

Space Toxicology has a rich and fascinating specialty that has remained largely unknown by the greater toxicology community. Spaceflight presents unique challenges and requires new and innovative methods to support human life as exploration ventures past low earth orbit into the various planets and other celestial bodies in our solar system. Exploring the unknown is at the core of scientific discovery and spaceflight toxicology is at the heart of sustaining the presence of human explorers in space.

ACKNOWLEDGEMENTS

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