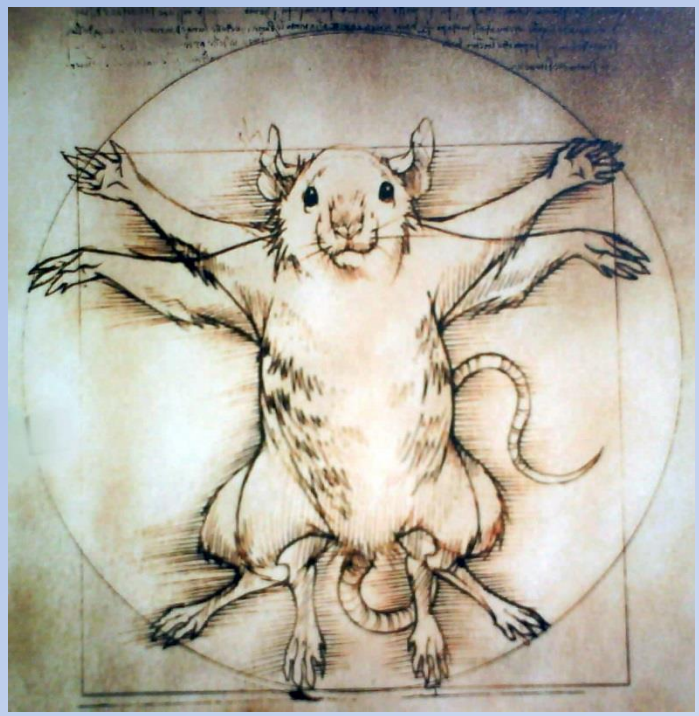
Lab Animal Allergies
A Common Problem in an Uncommon Place - The ISS



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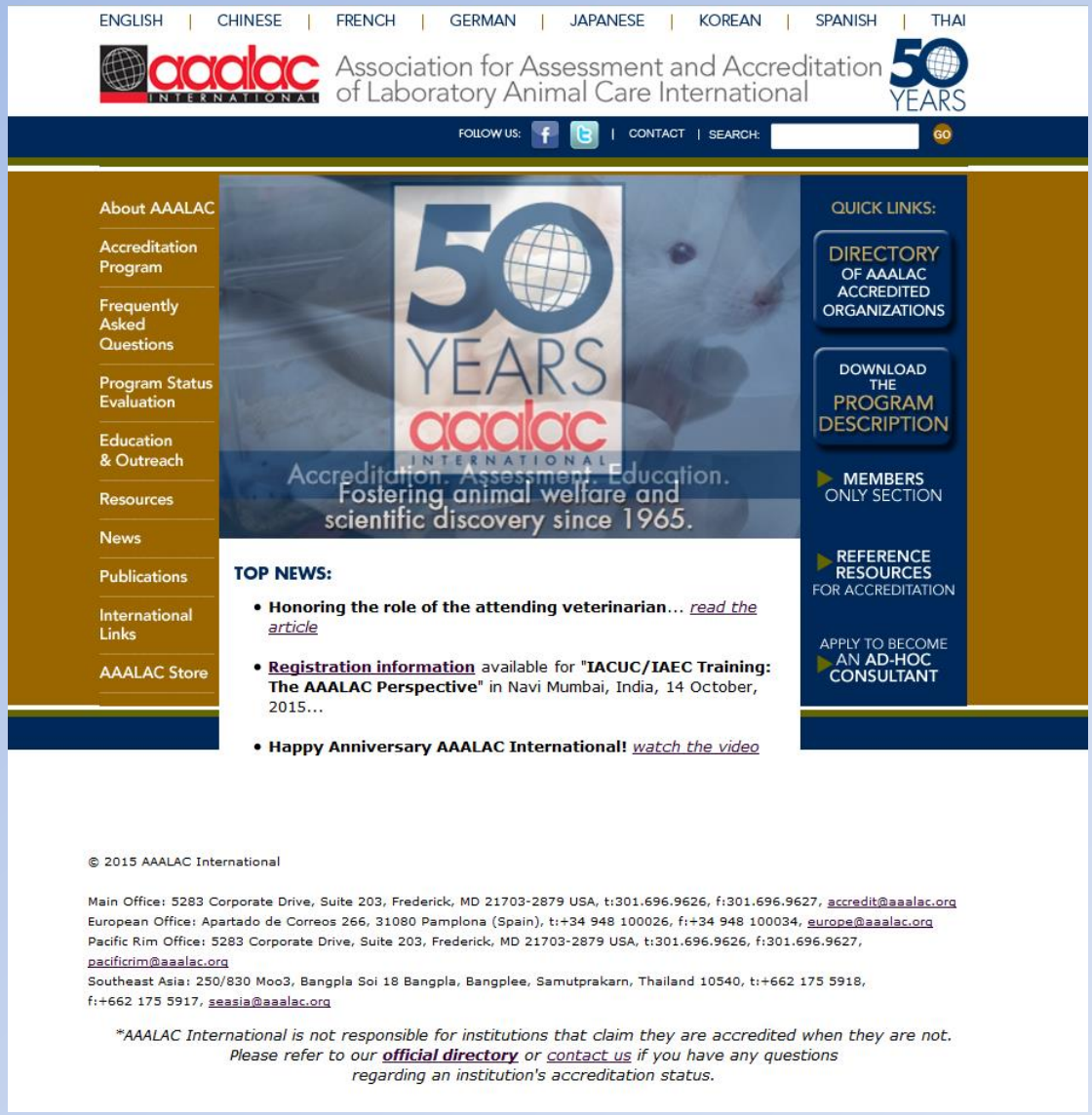


Lab Animal Allergies
The Risk

- Up to 40% of people newly exposed to lab animal allergens (allergy causing agent) develop some sort of allergic response after 2-3 years*
  - 30% develop allergies in the 1st year
  - 70% occur over the next 2 years
- Most astronauts will be new to this type work i.e. “newly exposed”

*Goodno LE, Stave GM., **Primary and secondary allergies to laboratory animals**, J Occup Environ Med. 2002 Dec;44(12):1143-52.

Past Rodent Research Missions

	RR1: National Lab - Novartis, and Verification of Rodent Research Hardware; SpX-4	RR2: National Lab - Novartis, SpX-6	
Launch Date	September 21, 2014	April 14, 2015	
Primary Science Objective	Rodent Research Hardware and Operations Validation	Evaluate muscle atrophy in microgravity and identify molecular pathways and targets that could be used to develop novel therapies for muscle disease.	
Mice	20 - C57BL/6 Female	20 - C57BL/6 Female	
Duration	33 days (NASA), 17.5 days (CASIS)	50d in habitat	
On-orbit Measurements		Bone densitometry scan	
Hardware	Standard RR Hardware	Standard RR Hardware	
Dissections	Hindlimb dissection & fixation (1 leg/mouse) Spleen dissection and preservation in RNAlater Liver dissection	Blood draw and separation Leg and eye fixation Leg dissection and freezing Carcass freezing	
Ops Timeline	CASIS: 5 mice/day, 2 days NASA: 10 mice/day (2 dissected and 8 intact carcasses frozen)	5 mice/group processed at each timepoint (week 1, 2, 4 and 8)	
Firsts	Rodent Habitats on ISS, Transporters on Dragon, AAU, dissections in MSG, new dissection table, 33 d on orbit,+ many more, tissue fixation kit, carcass freezing kit, daily health check with video downlink	Soft Tissue Fixation Kit and Cardiac Puncture Kit, 60 d on orbit, Bone densitometry with live mice, food bar changeouts, Water refill	
Mission Success Criteria	SS RR1 Research Implementation Plan, SSP 50957A		
Patches			

Continued on next page

Near-term Rodent Research Missions

	RR3: National Lab - Eli Lilly	RR4: National Lab - DoD	RR5: National Lab - UCLA
Current Launch Date	SpX 8: 1/3/16	SpX10: 6/10/16	SpX12: 12/17/16
Primary Science Objective	Evaluate effects of a drug aimed at preventing muscle loss	Characterize events associated with bone healing/tissue regeneration in a microgravity environment	Osteoporosis drug evaluation
Mice	20 – BALB/c Female (10-14 wks at launch)	40 – C57BL/6 male (10 wks at launch) with pre-flight surgery	40 - C57BL/6 female (12 wks old at launch)
Duration	45 days, return samples on SpX-9	Approx 28 days (minimum L+20d, max Dragon undock -7d)	60 days
On-orbit Measurements	Bone densitometry scan and Grip strength assessment	None	Bone densitometry scan
Dissections	Blood draw and separation, Leg fixation, Carcass freezing	Blood samples (frozen), Carcasses (Frozen), Fixed hind limbs (only 20, one leg from each mouse)	Cardiac puncture and blood collection Carcass frozen (MELFI). TBD whether for only 20 mice or all 40.
Pre-Launch	Grip Strength, injection, Bone Scan	Bone Defect Surgery & Therapy, tail tattoo, x-ray	Ovary removal surgery
Ops Timeline	Injections every 2 weeks. L+ 30d: grip strength and bone densitometry with recovery. L+45d: grip strength, bone densitometry, dissection. 7 consecutive days of crew time	Dissections start a minimum of L+20 days. All dissections must occur in 5 consecutive days and must be completed in time for all samples to return on SpX10	IP and SQ Injections to occur every 2 weeks on-orbit. L+4 to 5 weeks bone densitometry with recovery. Dissections at L+56d (min), bone densitometry scans just prior to euthanasia (dissections to occur in minimum possible consecutive days)
Firsts	Anesthesia Recovery, Grip Strength	40 mice. Male mice. Mouse enrichment (TBD), surgerized mice (mice with bone defects)	Possible live return Lid-based Food
Misc.		Direct GLACIER insert (Carcass and blood in the same ziplock bag) +4 MELFI fixed hindlimb (no fixative swap)	Change back to female mice

Male mice are more allergenic than females

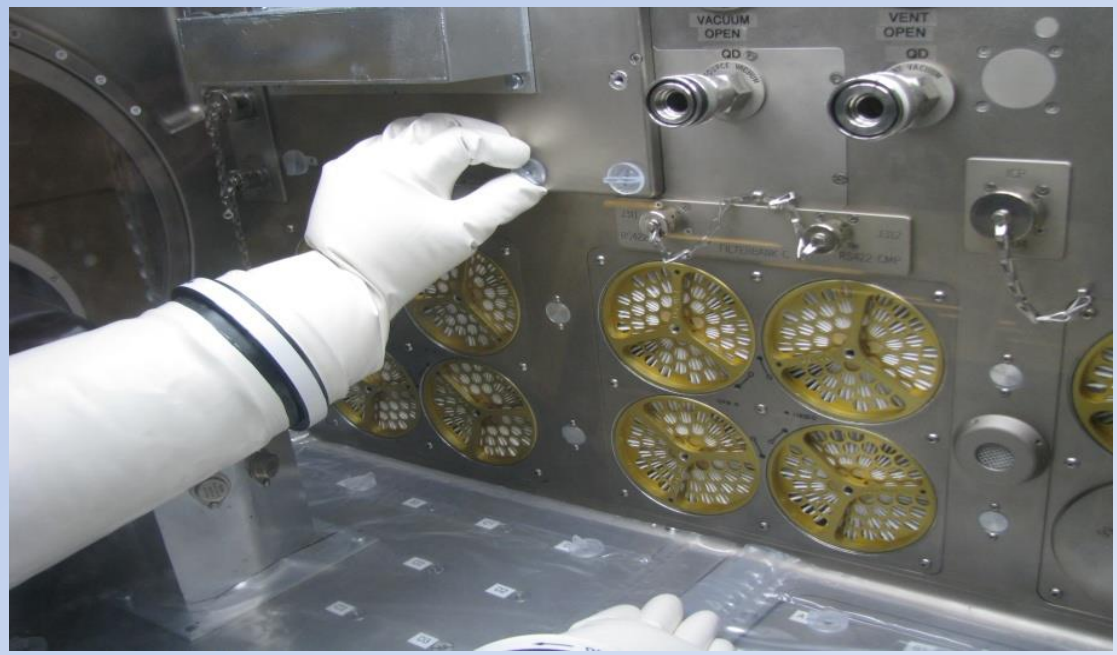
Tissues Collected/Planned

	Spleen	Liver	Hind Limbs	Blood	Eye	Carcass
RR1 (SpX-4)	X	X	X			X
RR2 (SpX-6)			X	X	X	X
RR3 (SpX-8)			X	X		X
RR4 (SpX-10)			X	X		X
RR5 (SpX-12)				X		X

Hind limbs to study muscle atrophy, bone loss, wound healing, bone repair (fixed and frozen)
Spleens to assess RNA quality, antibody response to vaccine (refrigerated then frozen)
Livers to study enzyme contents, gene expression, protein identification (frozen)
Blood to assess hormone changes at different time points, antibody response to vaccine (frozen)
Eyes to assess visual impairment issues (fixed)
Carcasses: remaining tissues available for Biospecimen Sharing Program (frozen)

Overview

- Historical perspective – animals in space
- Review medical knowledge base
- Review JSC's astronaut protection process



Animal Pioneers in Space

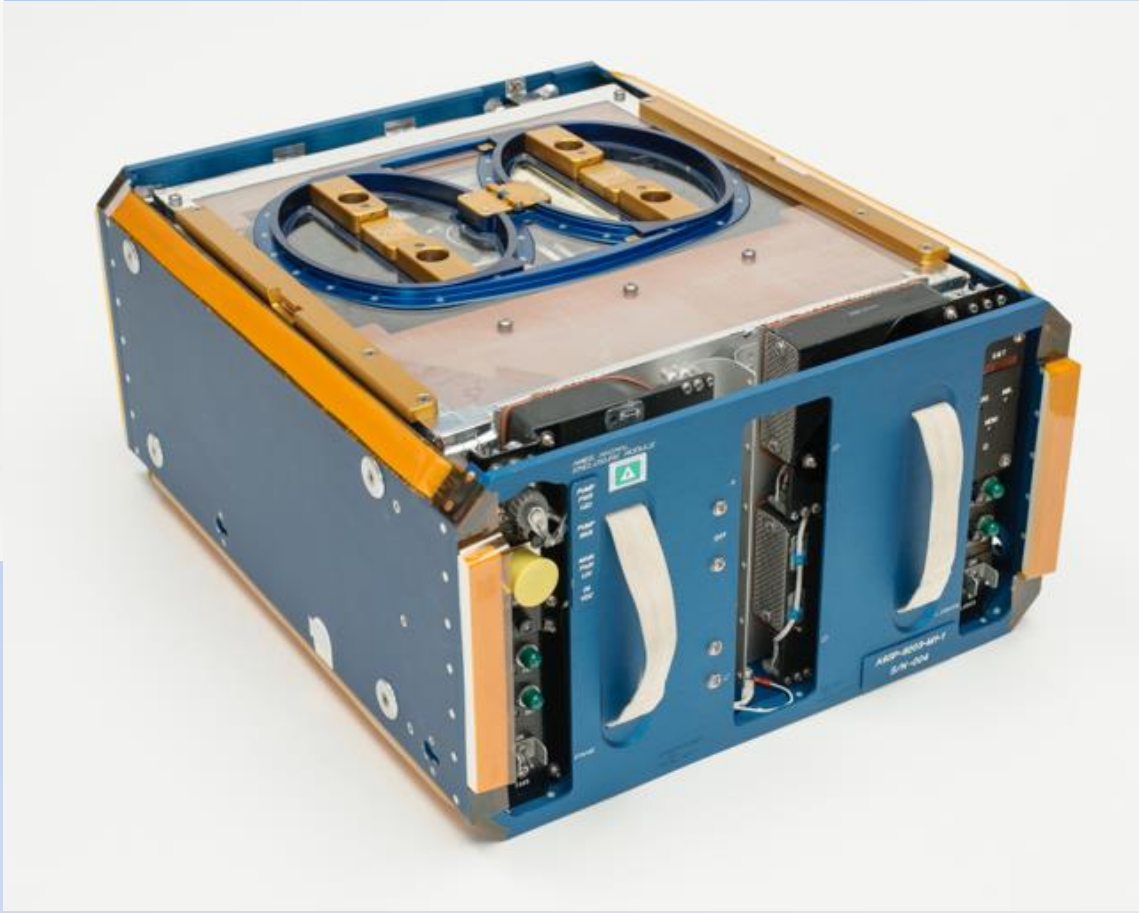
Habitat, Transporter, Access Unit

Photos courtesy of Ames Research Center, Janet Beegle, Rodent Research Project Manager

Habitat

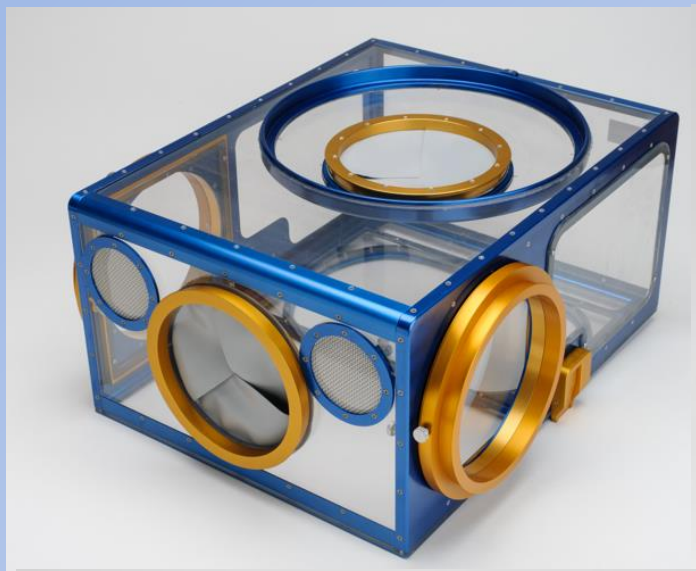
The Habitat is used to house the mice on the International Space Station. It holds 10 mice (5 per side) for up to 60 days. The Habitat includes food, water, airflow and filtration, lights for day/night cycle, and cameras for health checks from the ground.

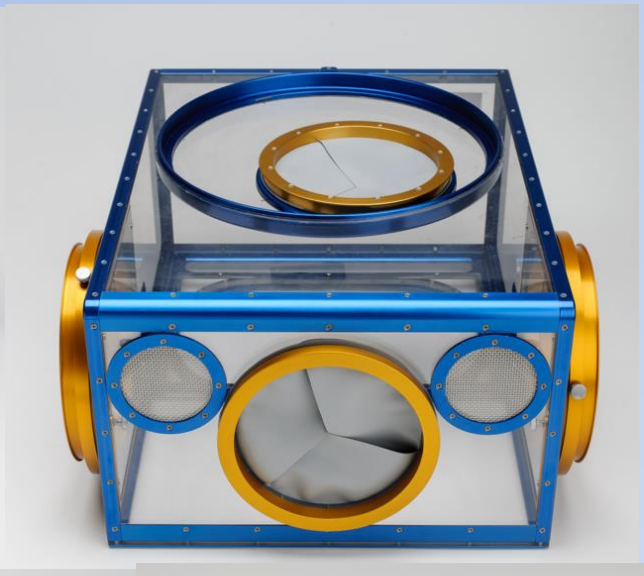
Transporter



The Transporter is used to transport the mice on SpaceX. Holds 20 mice (10 per side)

Access Unit



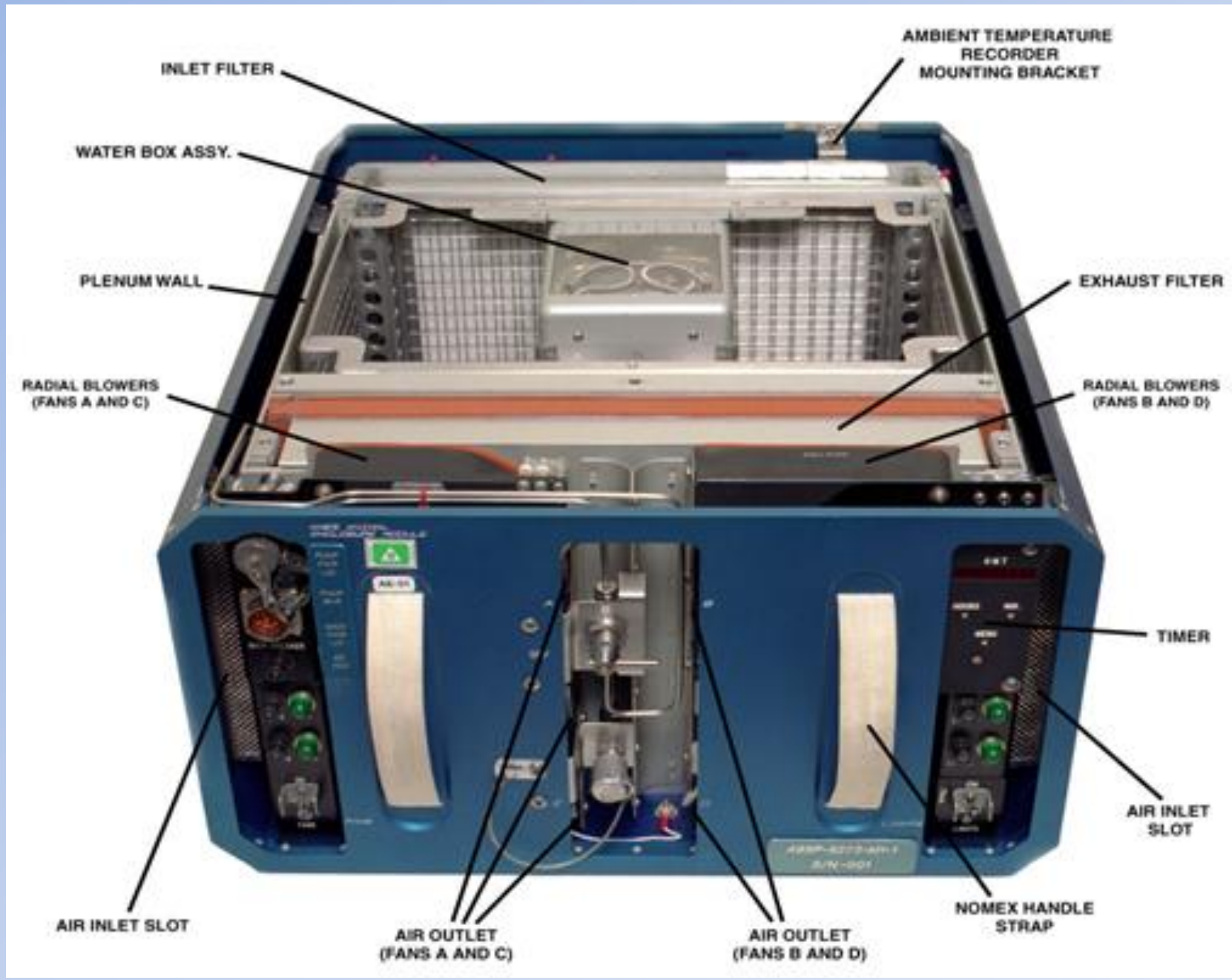


The Animal Access Unit is used to transfer the mice from the Transporter into Habitats and from the Habitat to the Microgravity Science Glovebox.

To make the transfer, the AAU mounts onto either the Transporter or Habitat.

Habitat w/Access Unit

AAU mounted on the Habitat


AMBIENT TEMPERATURE RECORDER MOUNTING BRACKET
INLET FILTER
WATER BOX ASSY.
PLENUM WALL
EXHAUST FILTER
RADIAL BLOWERS (FANS A AND C)
RADIAL BLOWERS (FANS B AND D)
TIMER
AIR INLET SLOT
AIR INLET SLOT
AIR OUTLET (FANS A AND C)
AIR OUTLET (FANS B AND D)
NOMEX HANDLE STRAP

ISS Filters

Summary of Human Experience with Lab Animals In Space prior to ISS

- We've sent animals into space without human presence in the space vehicle
- We've completed short duration missions (up to 18 days) with animals onboard manned vehicles, e.g. the space shuttle, but minimal handling of the animals.
- The actual animal handlers were ground based.

Compare and Contrast
Human Experience Base vs ISS Planned Use

- Astronauts expected to handle the animals
  - Experience base: Minimal
  - ISS Plan: Yes
- 24/7 exposure to animals
  - Experience base: Yes
  - ISS Plan: Yes
- Length of time living with the animals
  - Experience base: short duration
  - ISS Plan: long duration
- Space vehicle extensively cleaned between missions
  - Experience base: Yes
  - ISS Plan: No

Lab Animal Allergies Risk Numbers*

- Up to 40% of people newly exposed to lab animal allergens (allergy causing agent) develop some sort of allergic response after 2-3 years
  - 30% develop allergies in the 1st year
  - 70% occur over the next 2 years
  - Most astronauts will be new to this type work
- "Allergies" means
  - Itchy eyes
  - Itchy / runny nose (most commonly treated diagnosis)
    - aka allergic rhinitis (already present in ~30% of astro corps)
  - Asthma (least common but not rare, ~10% of the 40%)

*See references at end of presentation

Lab Animal Allergies
Risk Factors

- Atopy
  - Atopy* is the genetic predilection to produce specific immunoglobulin E (IgE) following exposure to allergens
  - Atopic dermatitis (0% of corps)
  - Allergic Rhinitis (~1/3 of corps)
    - Mostly allergies to pollens (not the same)
    - 2 individuals with allergies to pets (is a risk)
  - Asthma (0% of corps)

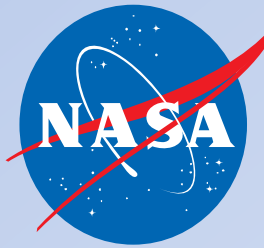
*Definition from UpToDate

Lab Animal Allergies Background Knowledge

- Animal allergens can be found in the urine (major source due to persistent proteinuria), saliva, hair and dander
  - Specific proteins have been identified e.g. the Mouse Urine Protein or "MUP"
- Routes of exposure include inhalation (primary route) and direct skin contact
- Type 1, immediate hypersensitivity (IgE)
- Allergens can reside on particles of > 0.5 to < 10 microns (respirable)
- Allergens may be carried in workers hair, on skin, or on clothing.

Ref: Gordon S, Preece R. **Prevention of Laboratory Animal Allergy**, Occupational Medicine, 2003, Vol. 53 No. 6, pp 371- 377.

Lab Animal Allergies
Avoiding Allergy Symptoms



- If you prevent exposure to the allergens then you will prevent the allergy symptoms (Goodno and Stave*, 0% when using PPE)
- Basic principle in occupational medicine – interrupt the exposure/symptom magnification cycle. Ex. Latex gloves.
- Basic immunology fact: first comes the sensitization, then the allergy.
  NOTE: sensitization ≠ allergy

*Goodno LE, Stave GM., **Primary and secondary allergies to laboratory animals**, J Occup Environ Med. 2002 Dec;44(12):1143-52.

Lab Animal Allergies
Airborne Concentrations

- No OSHA airborne particle standard
- *Institute of Occupational Medicine, UK (S. Gordon):*
  - Suggested risk of sensitization and development of symptoms to mice is increased MUP concentrations >5ng/m^3
- *Johns Hopkins University/Department of HSE:* <1ng/m^3

Astronauts and Mousetronauts

- Astronauts will undergo
  - Generic training during pre-assigned phase
  - Skills-based training 6-9 m prior to mission
  - Mission specific training 3 m prior to mission
- Wear PPE during training
  - Gloves worn during handling of mouse
  - Clean/disposable lab coat removed upon departure from lab
  - Respirator mask when in the lab

Astronaut Occupational Health Program (AOHP)

- Reviewed training program
  - Inspected training area and practices
  - Established PPE and use of vent hood
- Biomonitoring (blood testing) annually monitoring for sensitization
  - ImmunoCAP (serum assay)
    - Mouse epithelial and urine proteins

Animal Training Facility - Pre

Animal Training Facility - Post

Microgravity Science Glovebox Facility Hardware Overview

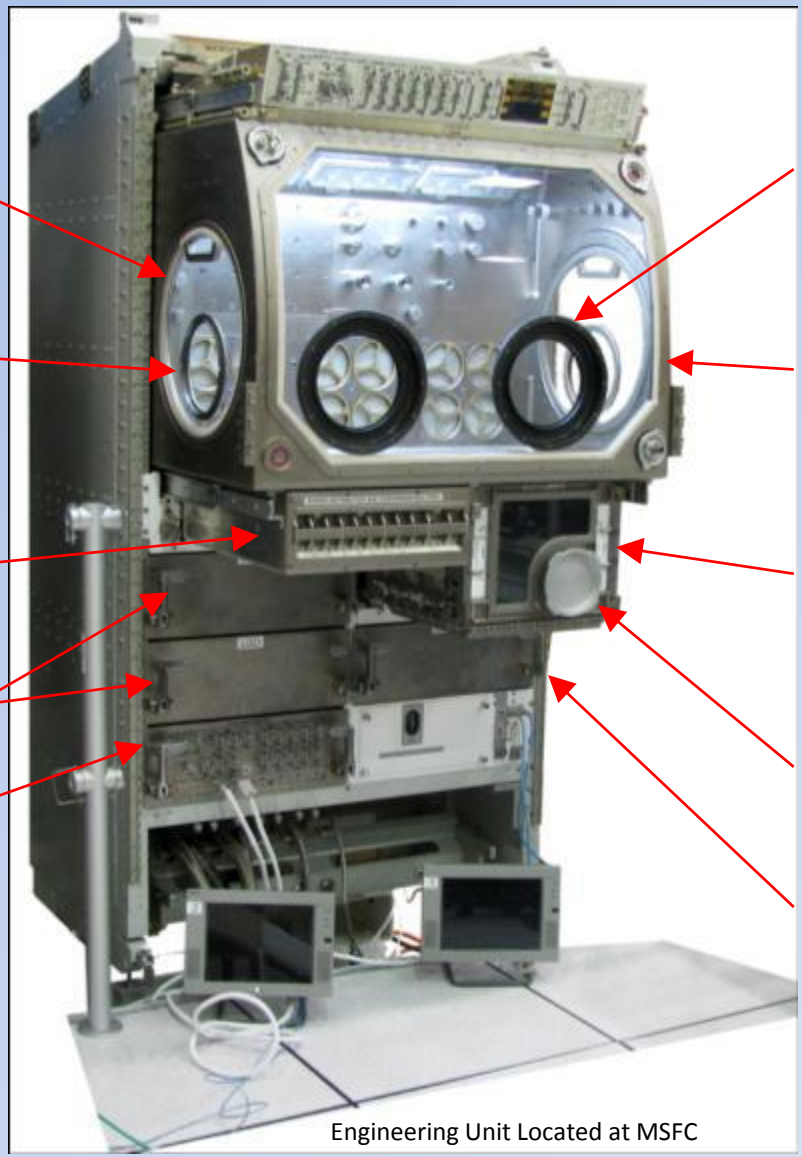
Removable Side Ports
16” diameter on both Left and Right sides for setting up hardware in Work Volume

Glove Ports
Four identical glove ports are located on the left and right side loading ports and the front window

DC Power Switching And Circuit Breakers

Stowage Drawers

Video System Drawer



Engineering Unit Located at MSFC

Front Window Glove Ports
Four 6” diameter glove ports can be fitted with any of three different sized gloves or blanks

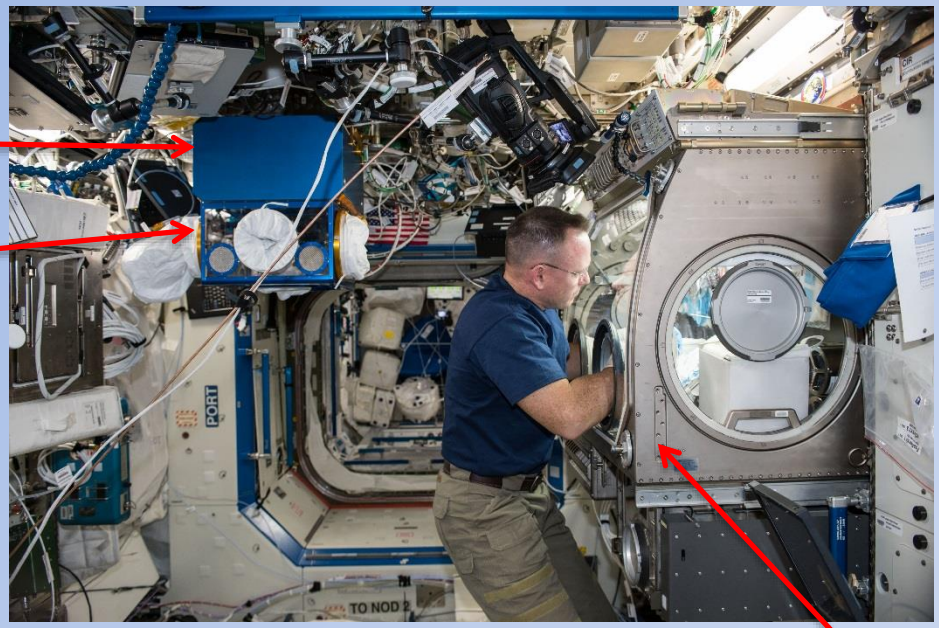
Core Facility
Retractable Core Facility includes the Work Volume, Airlock, Power Distribution & Switching Box, and the Command and Monitoring Panel

Airlock
Provides a “Pass Through” for hardware to enter the Work Volume without breaking Containment. The lid of the Air Lock opens up into the floor of the Work Volume

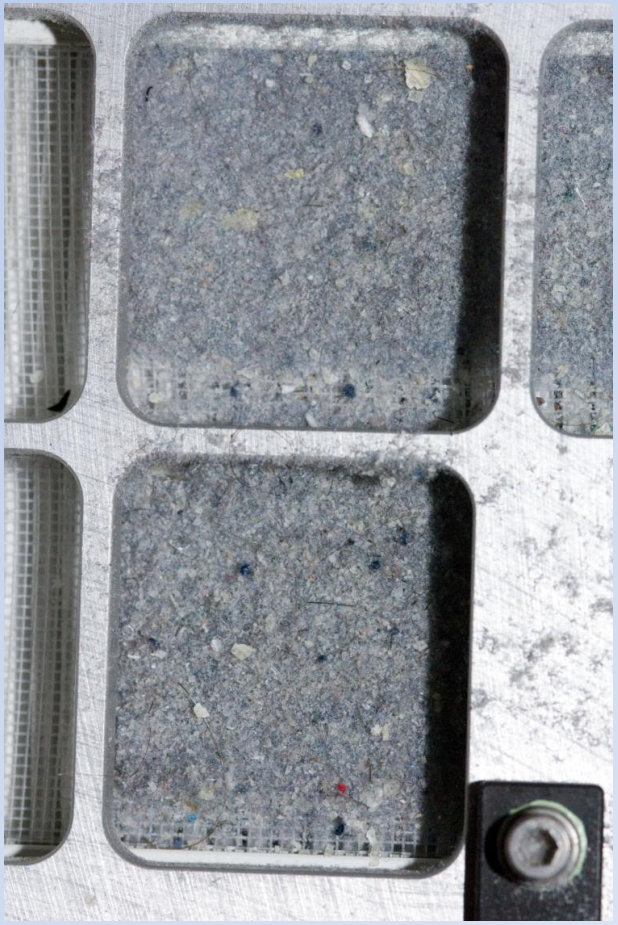
Airlock Glove Port with Blank
A Single 4” diameter glove port can also be fitted with any of three different sized gloves or a blank

Stowage Drawers

On-Orbit Configuration (US Lab)



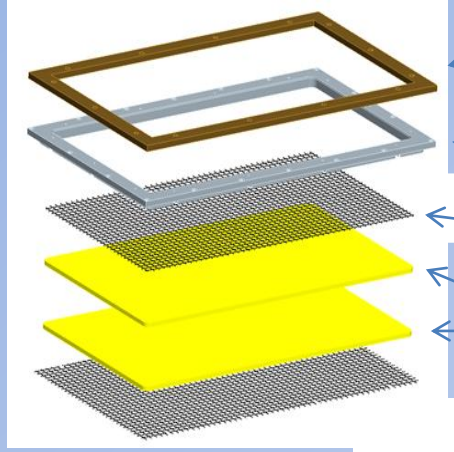
ISS HEPA Filters



- HEPA filtration is designed to minimize contaminants in air by controlling particulates (remove 99.97% of particulates >0.3 microns)
- Accumulated dust is complex (e.g. food residue, skin particles, etc.)

Rodent Research Habitat Long Duration Filter

(Exploded View)



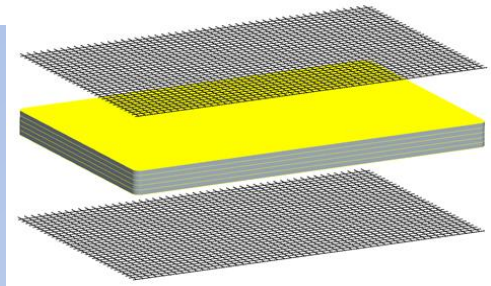
Sealing Gasket (Direct Interface with Habitat)

Aluminum Frame (Frame is re-usable)

4x4 Mesh Screen

Bondina (20ml of Phosphoric Acid)
Sorbent (20ml of Phosphoric Acid)

Top Cover Assembly



4x4 Mesh
Sorbent Pad
Bondina (20ml of Phosphoric Acid)
Sorbent Pad
Zeolite
Sorbent Pad
4x4 Mesh Screen

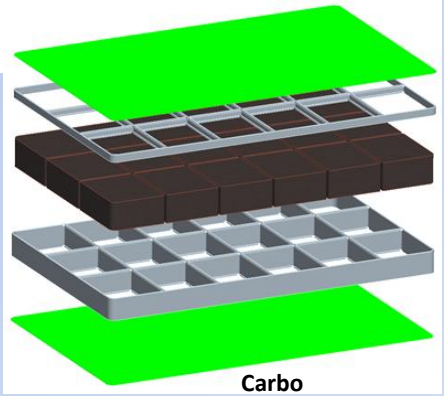
Sorbent Pad

Mus.m-1 average 13014 ng/25 cm^2

~99% reduction in Mus.m-1

(Sorbent Pad samples compared to Main Housing samples)

Mus.m-1 average 190 ng/25 cm^2



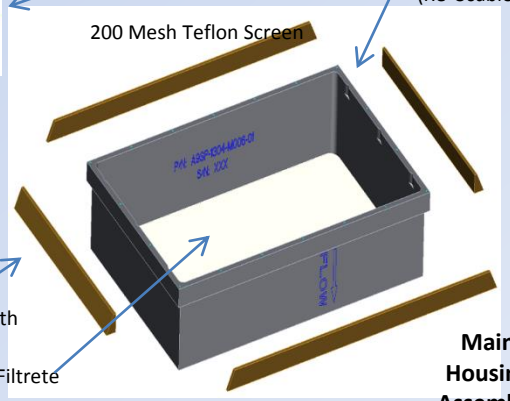
200 Mesh Teflon Screen

3D Printed Fame (Top Half)

Chemically Treated Activated Carbon

3D Printed Frame (Bottom Half)

Carbon Bed Assembly



Aluminum Frame (Re-Usable)

200 Mesh Teflon Screen

Sealing Gaskets (Direct Interface with Habitat)

Filtrete

Main Housing Assembly

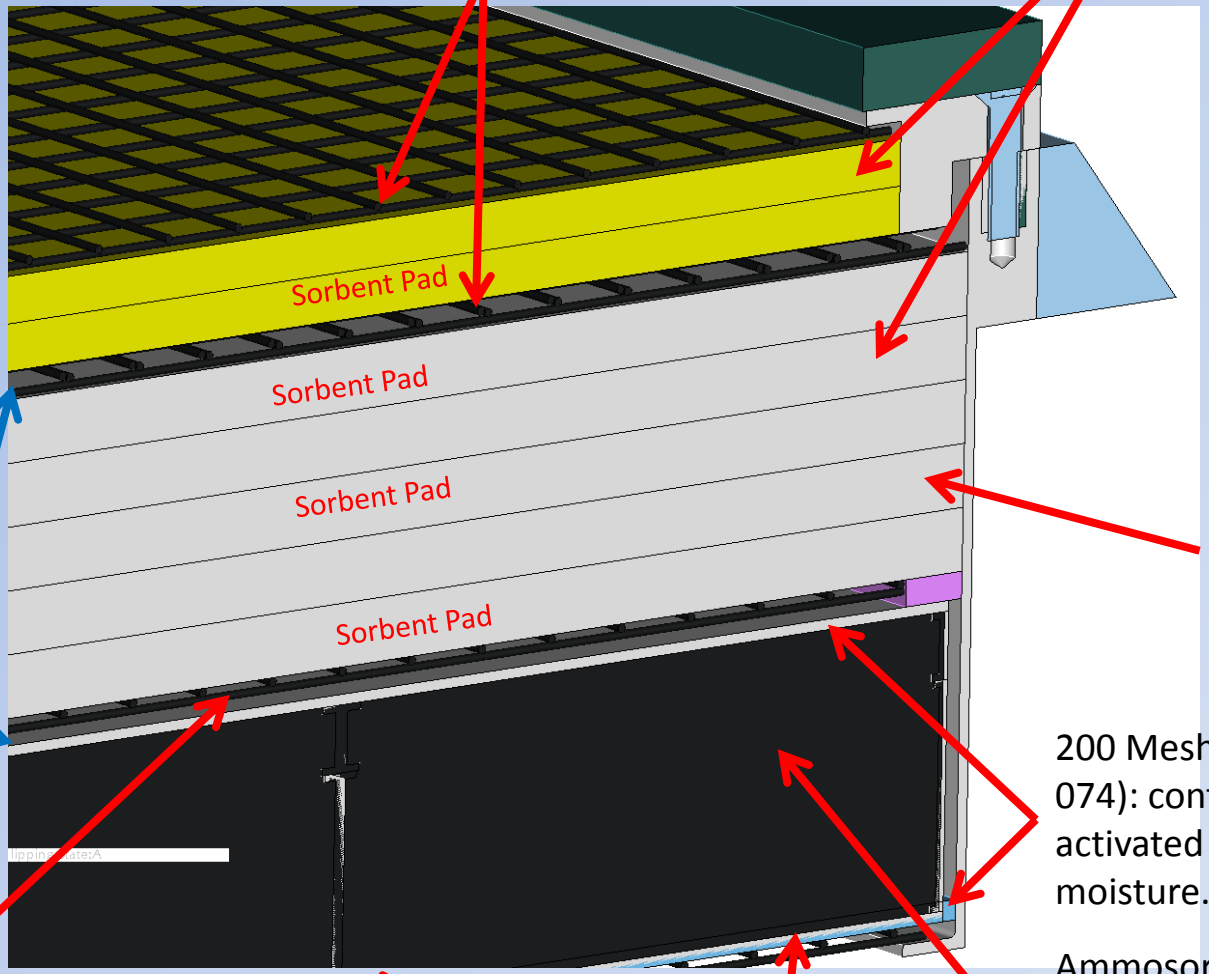
Diagram courtesy Ames Research Center

Rodent Habitat Exhaust Filter

Airflow

4x4 Stainless Steel Mesh: internal habitat fecal barrier

Bondina (AH-01880): suspends phosphoric acid, spreads liquids for drying.



Universal Sorbent Pad (M-YH): absorbs liquids, treated with phosphoric acid. (20-23g per sheet)

Air Gap: eliminates capillary action of fluid between components. (~0.07")

Zeolite (Z3264): tuned to react with ammonia, absorption.

200 Mesh Teflon Screen (13-074): contains ands protects activated carbon from moisture.

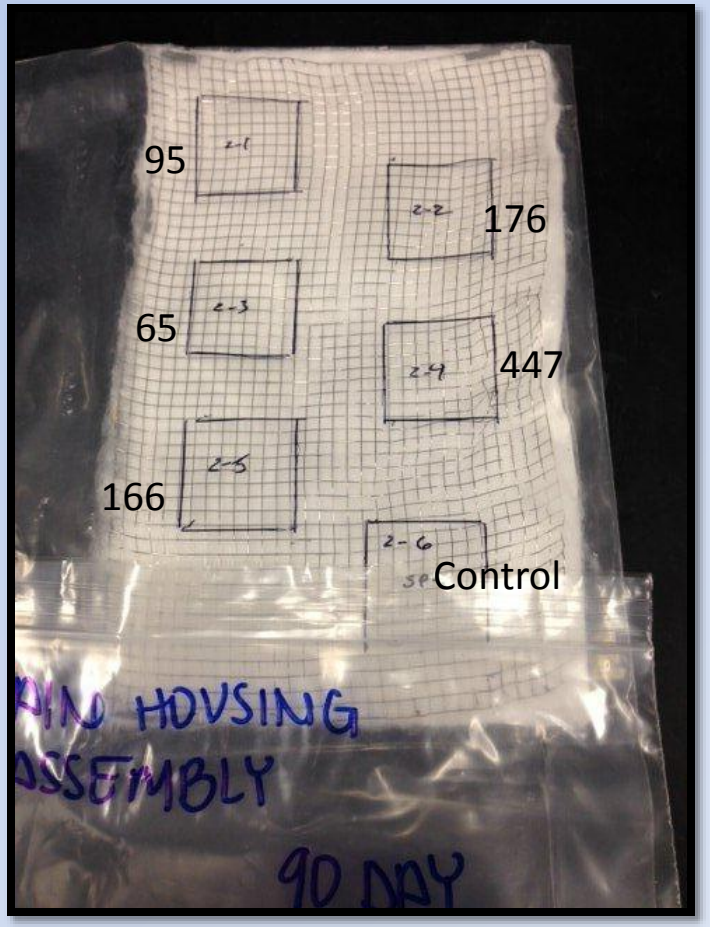
Ammosorb Activated Carbon (1.0-3.0mm): phosphoric acid treated for the removal of lightweight organic compounds

4x4 Stainless Steel Mesh

G200 Filter Media (E668): captures 94.8% of particles 0.1 micron and larger

AMES 90-Day Rodent Habitat Filter Evaluation

Amount of Mus.m-1 per filter sample (ng/25cm^2)



Lab Animal Allergies and Space Missions

- Terrestrial data provides a good idea of what happens to people that go into this line of work
- This data cannot be expected to translate 100% to ISS environment
  - Microgravity/Airflow differences
  - Closed loop environment system
  - 24 hour exposures for months at a time
    - More like owning a pet in a very clean home IF the hardware works as designed
  - Immune system dysfunction
- We must prepare for the worst while hoping for the best

POTENTIAL FAILURES

Release of allergens into the closed ISS atmosphere

Animal bites – protective gloves can go over nitrile, but optional because some find them bulky and awkward. Concern for infection.

Needle sticks – similar concerns to any medical environment, plus dirty animals.

Sharps – scalpels, scissors, bone cutters, dirty animals *in microgravity!*

Allergic reactions

- mild – itchy watery eyes, sneezing
- mod – sinus congestion, skin rashes
- severe – respiratory distress, vascular headache

MEDICATIONS

Desired: Sufficient medications for six crewmembers

1. Oral and Ophthalmic antihistamines
2. MDIs - Short and Long acting B-Agonists, Steroid
3. Topical Steroids
4. Oral and IM steroids
5. Nasal steroid and saline flush (seamist)
6. Antiobiotics - Oral, IM, IV Pasteurella, Streptobacillus Monoliformis
7. Imitrex/Ergotamines?

References

1. **Laboratory Animal Allergy Prevention Program (LAAPP)**, National Institutes of Health Division of Occ Health and Safety, revised May 24, 2011.
2. Bush RK, Stave GM; **Laboratory Animal Allergy: An Update**; ILAR Journal, 2003, 44:1.
3. Goodno LE, Stave GM., **Primary and secondary allergies to laboratory animals**, J Occup Environ Med. 2002 Dec;44(12):1143-52.
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5. Stave GM, Darcey DJ. **Prevention of Laboratory Animal Allergy in the United States**, J Occup Environ Med. 2012 May, Vol. 54, No. 5, pp 558-563.