Acute Radiation Risks and Countermeasures for Space Radiation

Francis A. Cucinotta

NASA, Lyndon B. Johnson Space Center
Houston, TX

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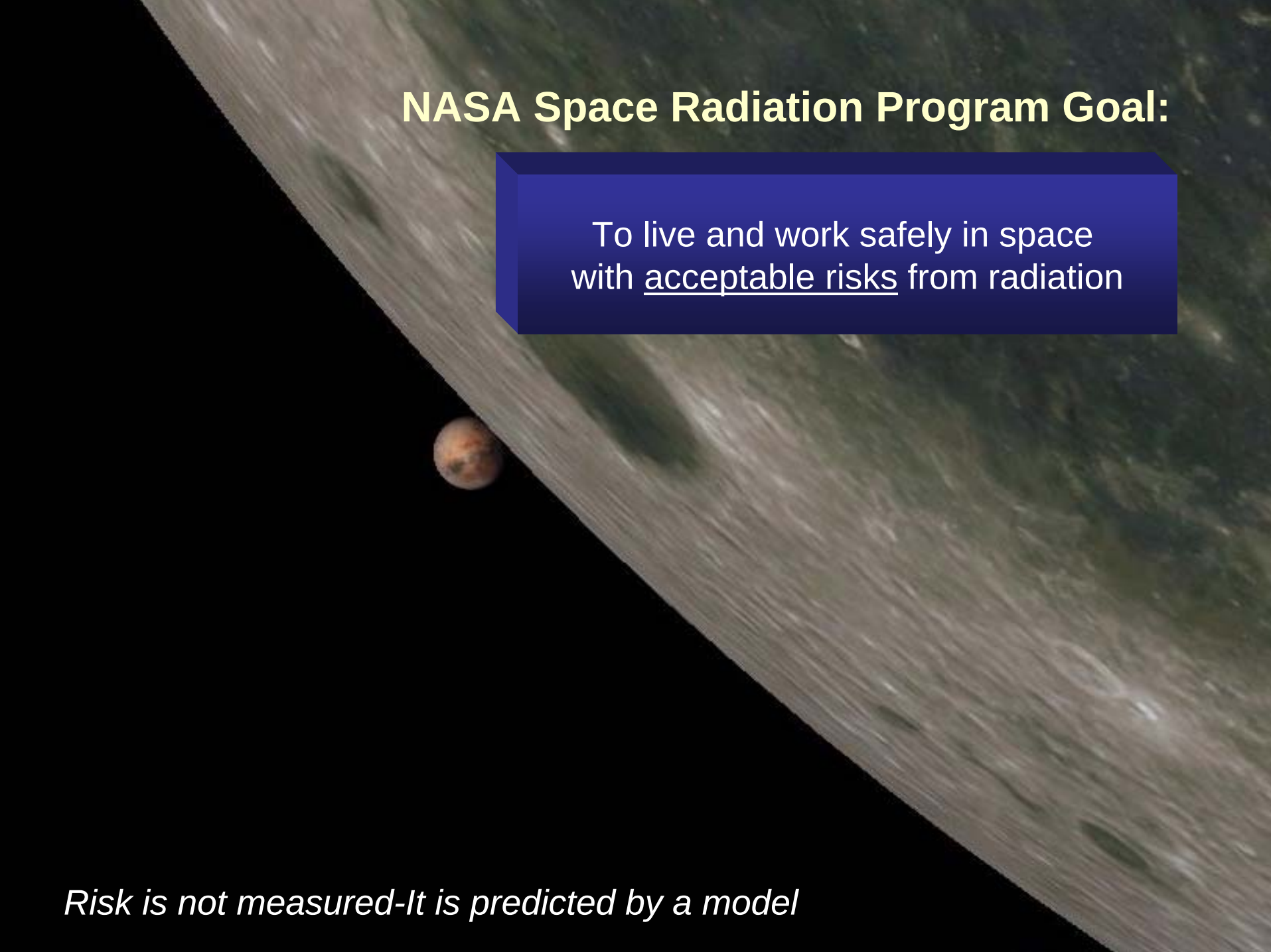


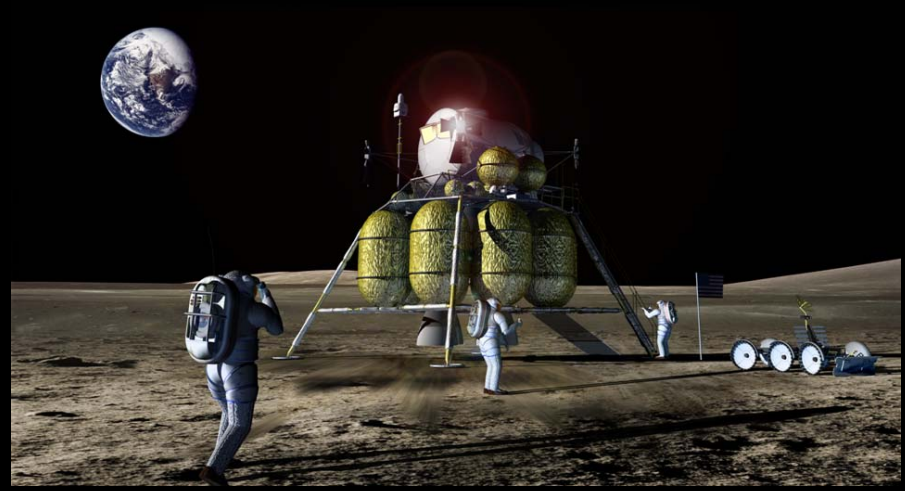
NASA Space Radiation Program Goal:

To live and work safely in space
with acceptable risks from radiation

Risk is not measured-It is predicted by a model

The NASA Vision for Space Exploration

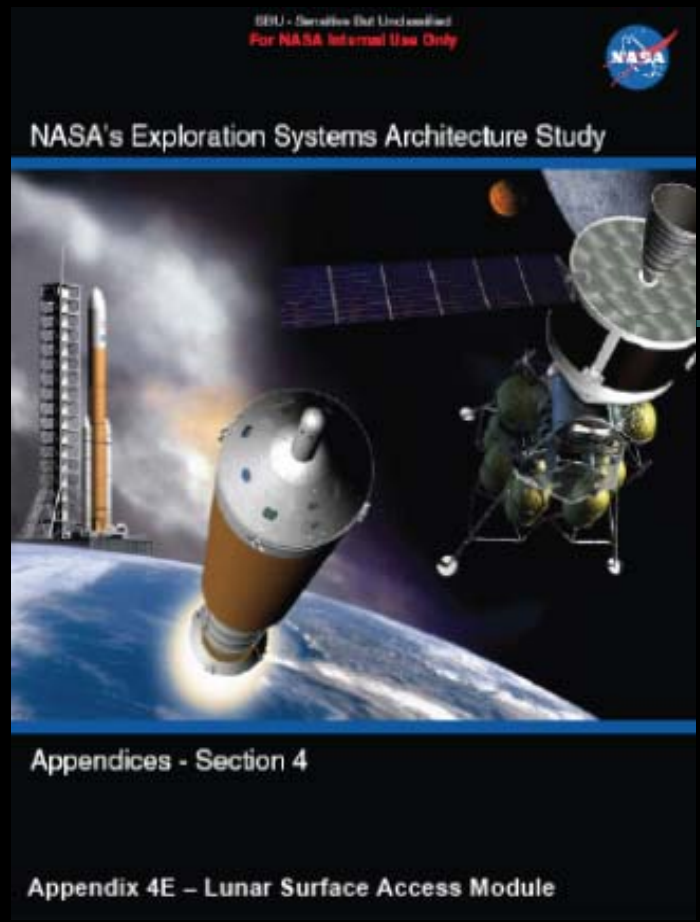
- NASA will carry out missions returning to the moon in next decade
  - Sortie missions ~14 days by 2020
  - Long duration missions up to 240 days by 2022
- Missions to Mars will occur towards 2030 building on the lunar program
- Radiation protection requirements including dose limits for lunar missions are now being formalized
  - Protection against large solar proton events are a major near-term goal
- Proposed NSBRI Acute Countermeasures Team requires Risk initial assessment focus



Cucinotta and Durante, *The Lancet- Oncology* (06)
courtesy of John Frassanito and associates

Constellation Program

- New NASA Program for human exploration missions
  - Near term focus development of Crew Exploration Vehicle replacing Space Shuttle for missions to the ISS and onto moon



Integrated Risk Projection

Mitigation:

- Shielding materials

- Radioprotectants

-Pharmaceuticals

Space Radiation Environment

Radiation Shielding

Initial Cellular and Tissue Damage
DNA breaks, tissue microlesions

DNA repair, Recombination,
Cell cycle checkpoint, Apoptosis, Mutation,
Persistent oxidative damage, & Genomic Instability

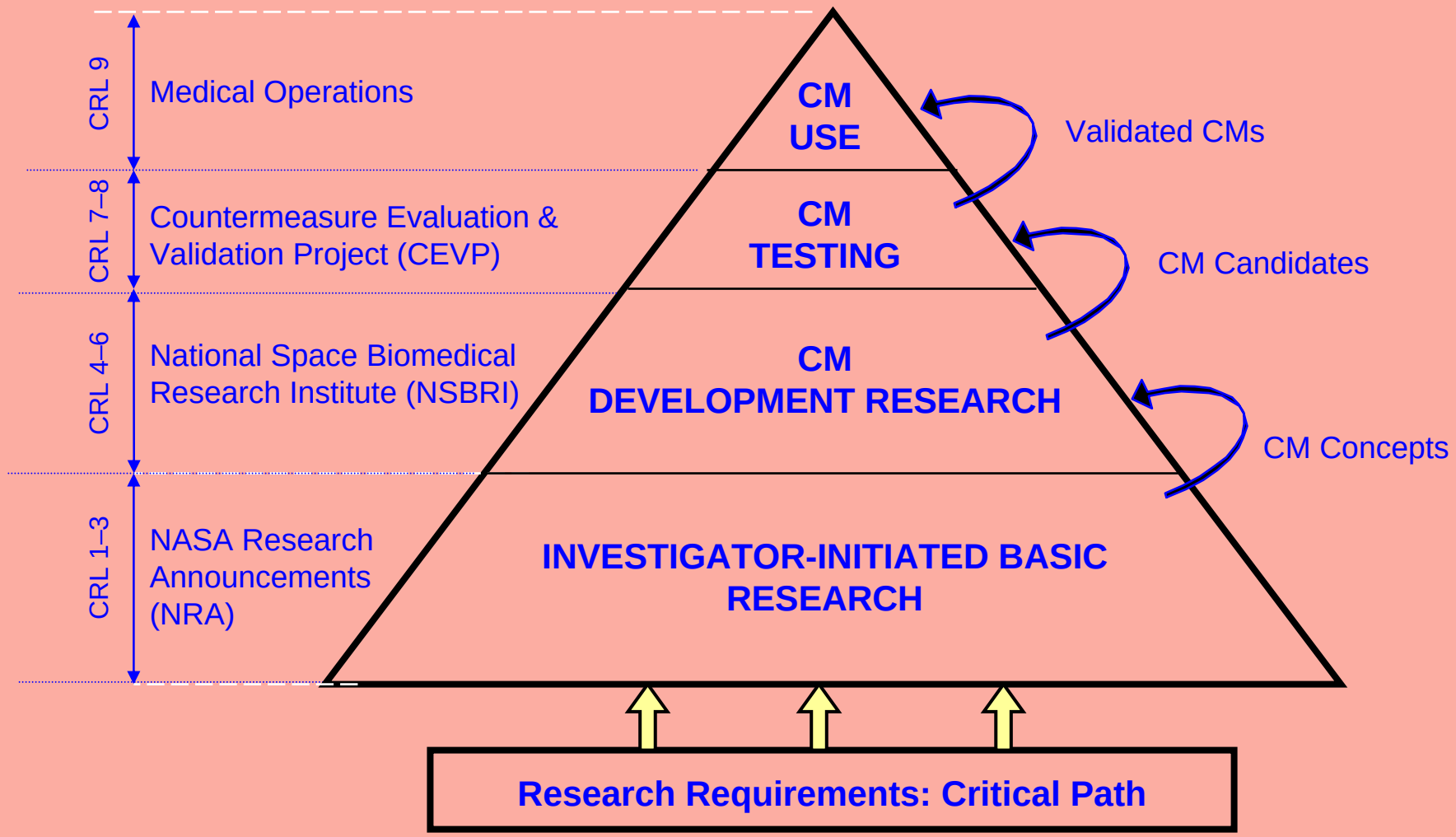
Tissue and Immune Responses

Risks:
Chronic: Cancer, Cataracts,
Central Nervous System,
Heart Disease
Acute: Lethality, Sickness,
Performance

Risk Assessment:
-Dosimetry
-Biomarkers
-Uncertainties
-Space Validation

$Risk_j$
(age,sex,mission)

Countermeasure Development Process



The Space Radiation Environment

Solar particle events (SPE) (generally associated with Coronal Mass Ejections from the Sun):

- medium to high energy protons
- largest doses occur during maximum solar activity
- not currently predictable
- MAIN PROBLEM: develop realistic forecasting and warning strategies

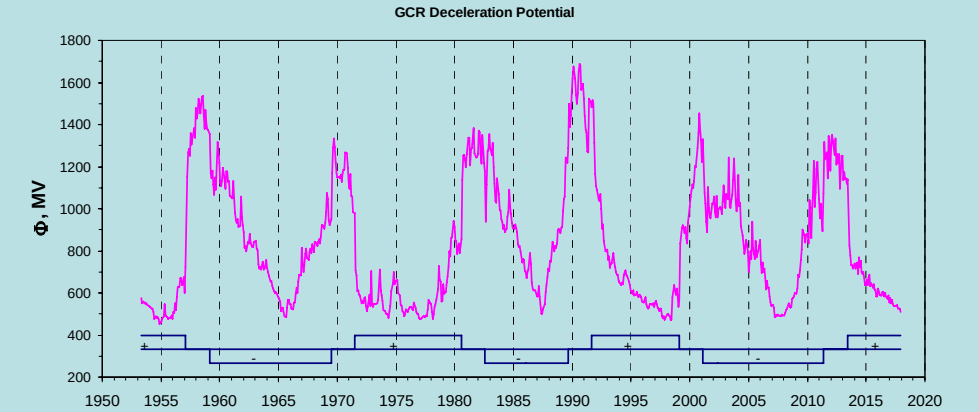
Trapped Radiation:

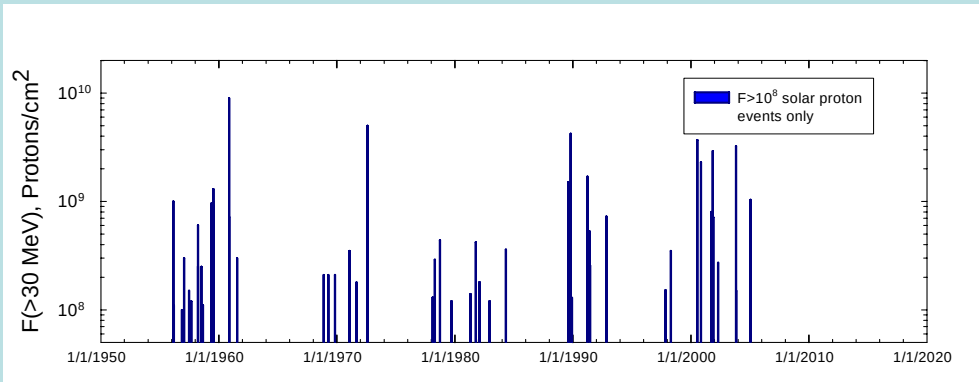
- medium energy protons and electrons
- effectively mitigated by shielding
- mainly relevant to ISS
- MAIN PROBLEM: develop accurate dynamic model

Galactic Cosmic Rays (GCR)

- high energy protons
- **highly charged, energetic atomic nuclei (HZE particles)**
- not effectively shielded (break up into lighter, more penetrating pieces)
- abundances and energies quite well known
- MAIN PROBLEM: biological effects poorly understood but known to be most significant space radiation hazard

Times of Occurrence of Large SPE's





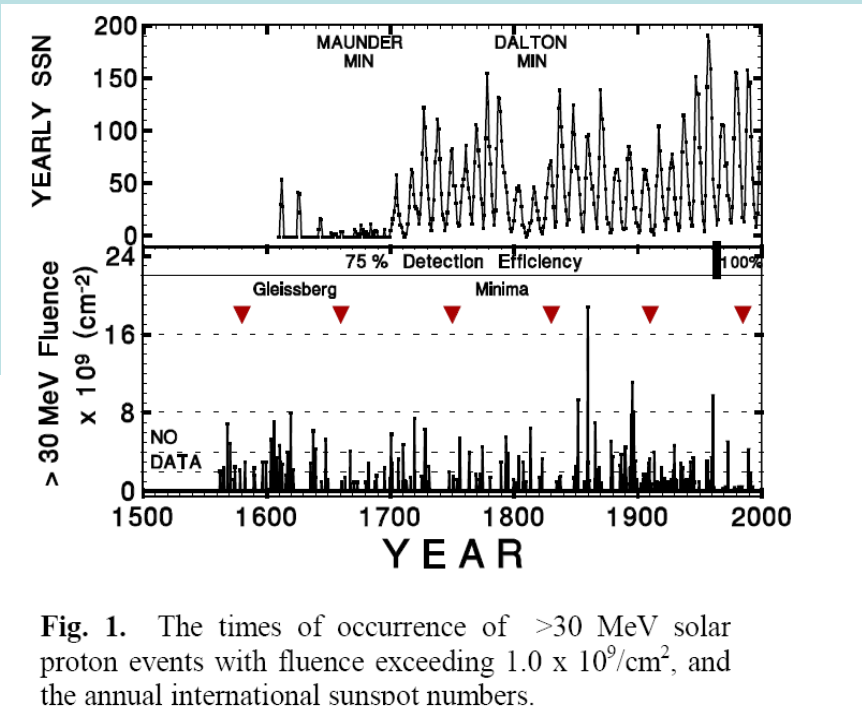


Fig. 1. The times of occurrence of >30 MeV solar proton events with fluence exceeding 1.0 x 10^9/cm^2, and the annual international sunspot numbers.

Modern Era (1956-2005)

Recent Era (1550-2000)
McKracken et al

Acute Radiation Risks Research

- Overall Objectives
  - Accurate Risk assessment models support
    - **Permissible Exposure Limits (PEL) Determination**
    - **Informed Consent Process**
    - **Operational Procedures**
      - Dosimetry
      - EVA timelines
      - Solar Forecasting Requirements
    - **Shielding Requirements**
    - **Countermeasure (CM) Requirements**
- Approach
  - Probabilistic Risk Assessment applied to Solar Particle Events (SPE)
  - Models of acute risks used to evaluate acute CMs for SPE and Lunar Surface conditions

Overarching Question for Proposed NSBRI Acute Radiation Risks Team?

- For which acute risks are biological countermeasures needed?
  - Risk assessment research and data for appropriate Animal models needed to answer this question
  - Appropriate experimental risk models should be used for testing of CM effectiveness
- What are the most promising high CRL Biological Countermeasures for Acute Risks of concern to NASA?

Major Questions for Acute Risk Models

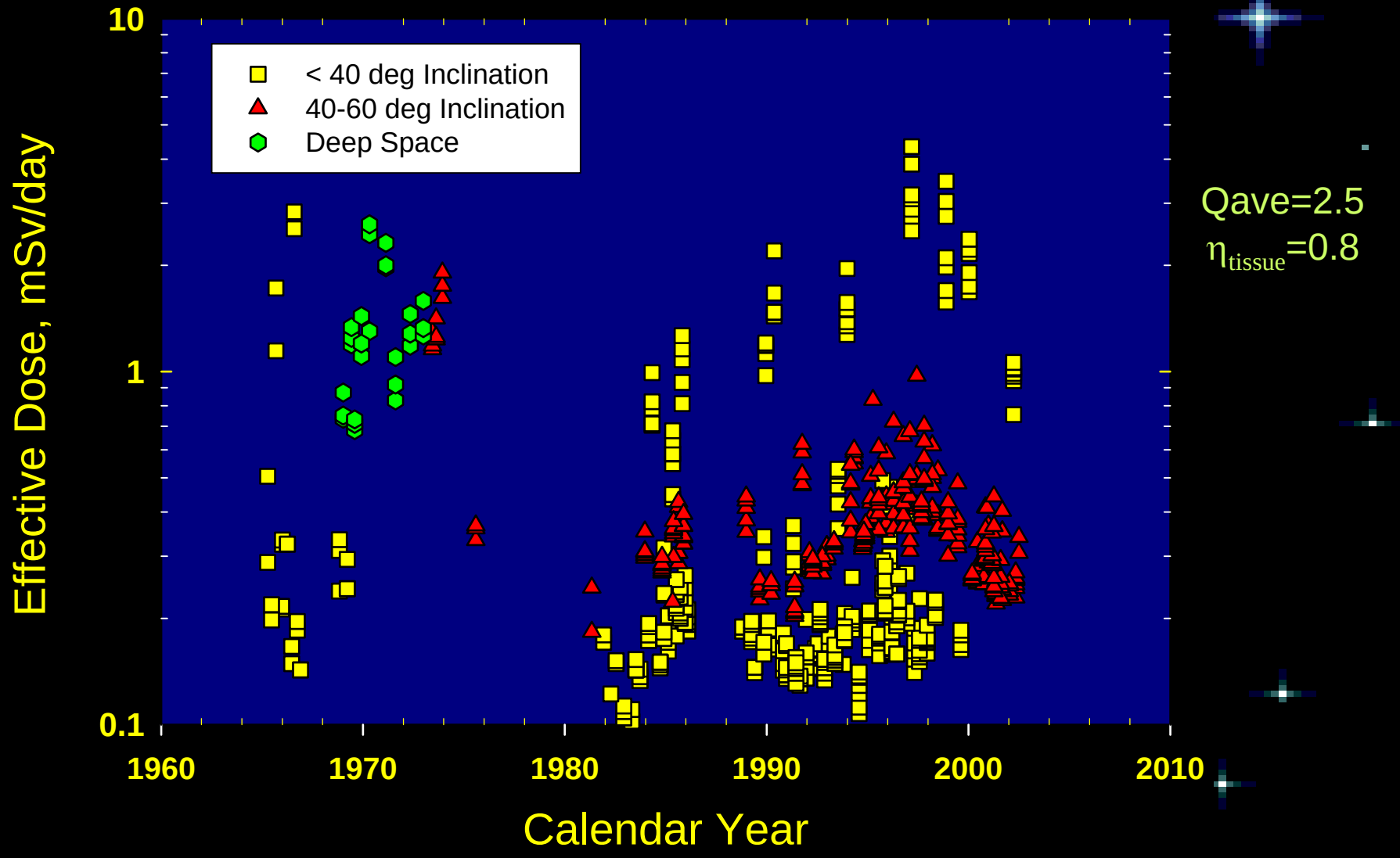
- What are the dose-rate modification (DRM) effects for SPE Acute risks?
- What are the RBE's for protons and secondaries?
- How do DRM and RBE's vary with Acute risks?
- Are there synergistic effects from other flight stressors (microgravity, stress, bone loss) or GCR on Acute risks?
- Is the shape of dose-response for Acute risks altered for any of the above, especially at P~10%?
- Are there individual variations at low P~10% Acute risk?
- For which Acute risks are countermeasures needed?
- How can the effectiveness of Acute countermeasures be evaluated and extrapolated to Humans?

BFO Limits

- Historically NASA Short-term limits are stated for acute risks but in actuality they are to both limit life-shortening while preventing any acute risks
- NRC Limit (1970) basis was for Reactor environment at high altitude (>500 km) not to prevent Prodromal risks of death
- NRC rationale:
  - Below 1 rem/day rate of injury and recovery are in equilibrium (steady state)
  - Thus over 1-year daily rate should be less 0.2 to 0.4 rem/day
  - Thus do not exceed 75 rem/yr or 35 rem/quarter

  "…The quarterly exposure should be restricted further so that accumulation in a single prompt exposure does not exceed 25 rem... no demonstrable effect….Exposure at the reference risk level, therefore may impose an acturial risk of loss of 0.5 to 3.0 years from the normal 40 to 45-yr after expectation of life for the age group under consideration"
- NCRP in 2000 recommend use of Gray-equivalent based on RBE ad Human geometry model to replace 5-cm depth dose

Crew Doses on Past Space Missions

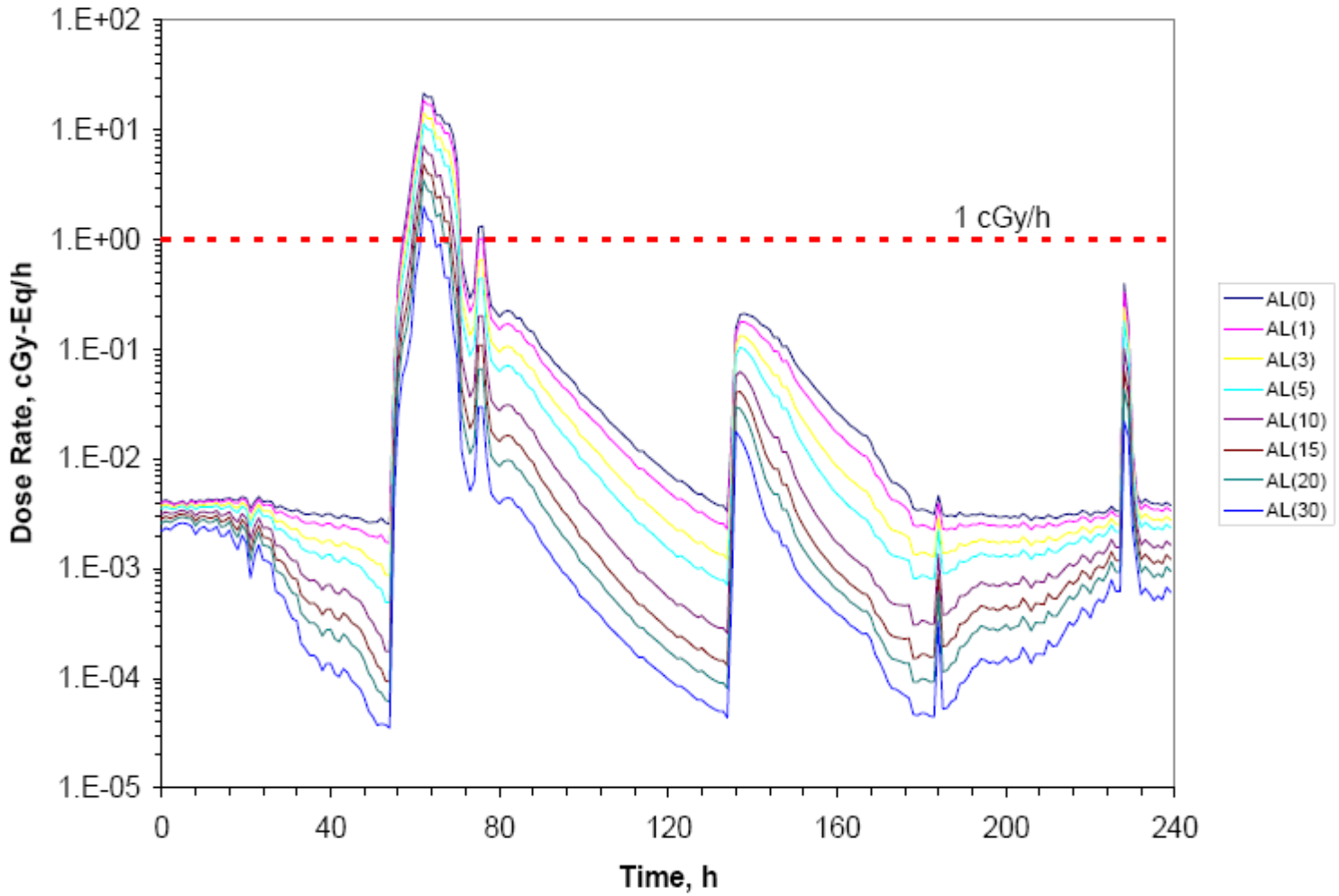


Acute Risks

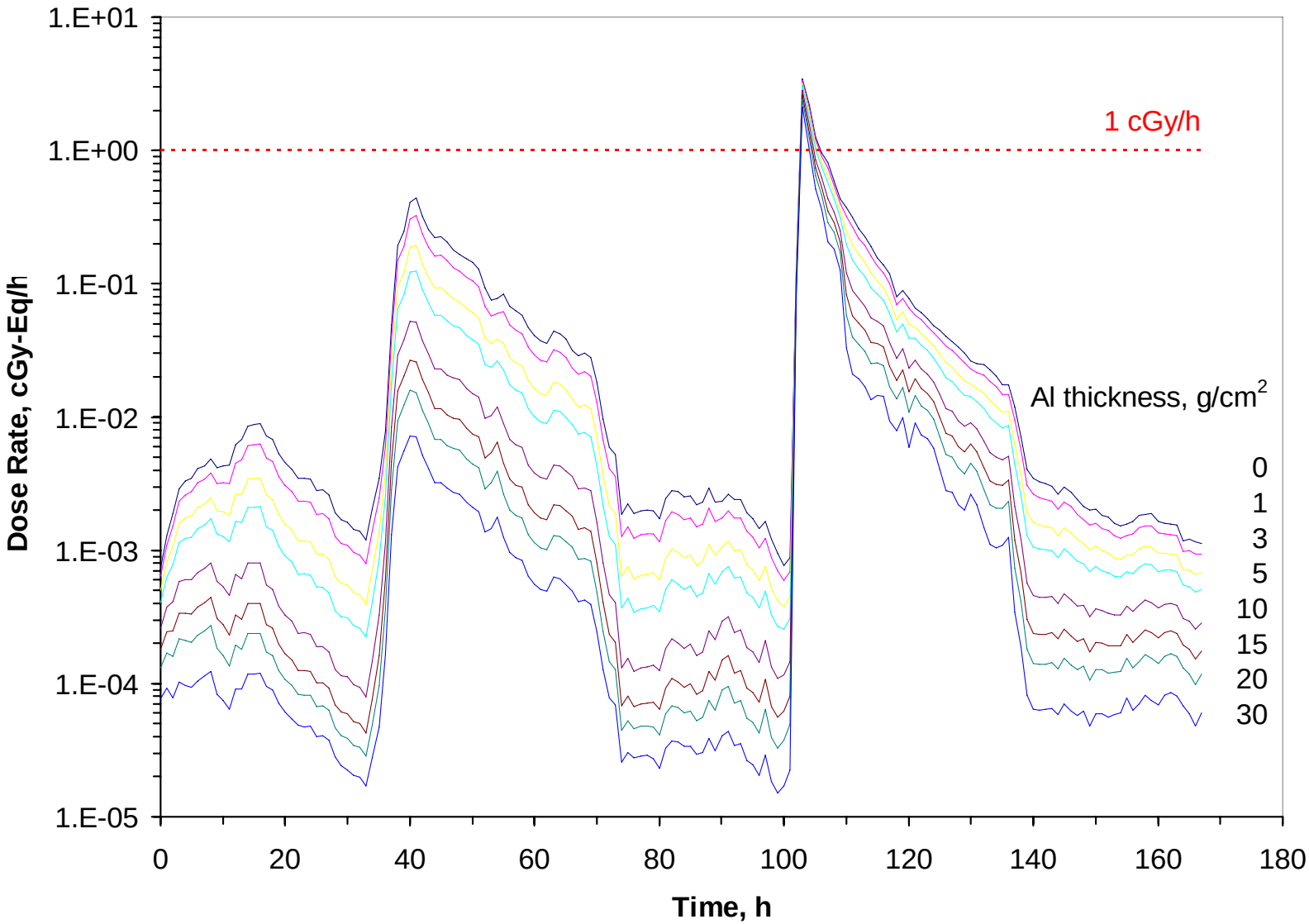
	ED_{50} γ-rays	ED_{50} Solar protons*
Death		
– Blood Marrow Failure	3.0 Gy	4 to 6 Gy-Eq (LDR)
– Gut Death	8.0	>12
– CNS	>10	>10
– Lung	>20	>20
Radiation Sickness/Damage		
– Anorexia	1.0, Gy	?, Gy-EQ
– Fatigue	1.5	?
– Vomiting	1.8	?
– Nausea	1.4	?
– Skin Damage	5	?
– Blood Count Changes	0.2	>0.2
– Sterility	0.4	?
	0.3	?

>>Dose-rate modifiers for γ-rays and especially protons poorly known

Dose-Rates to BFO for August 72 SPE

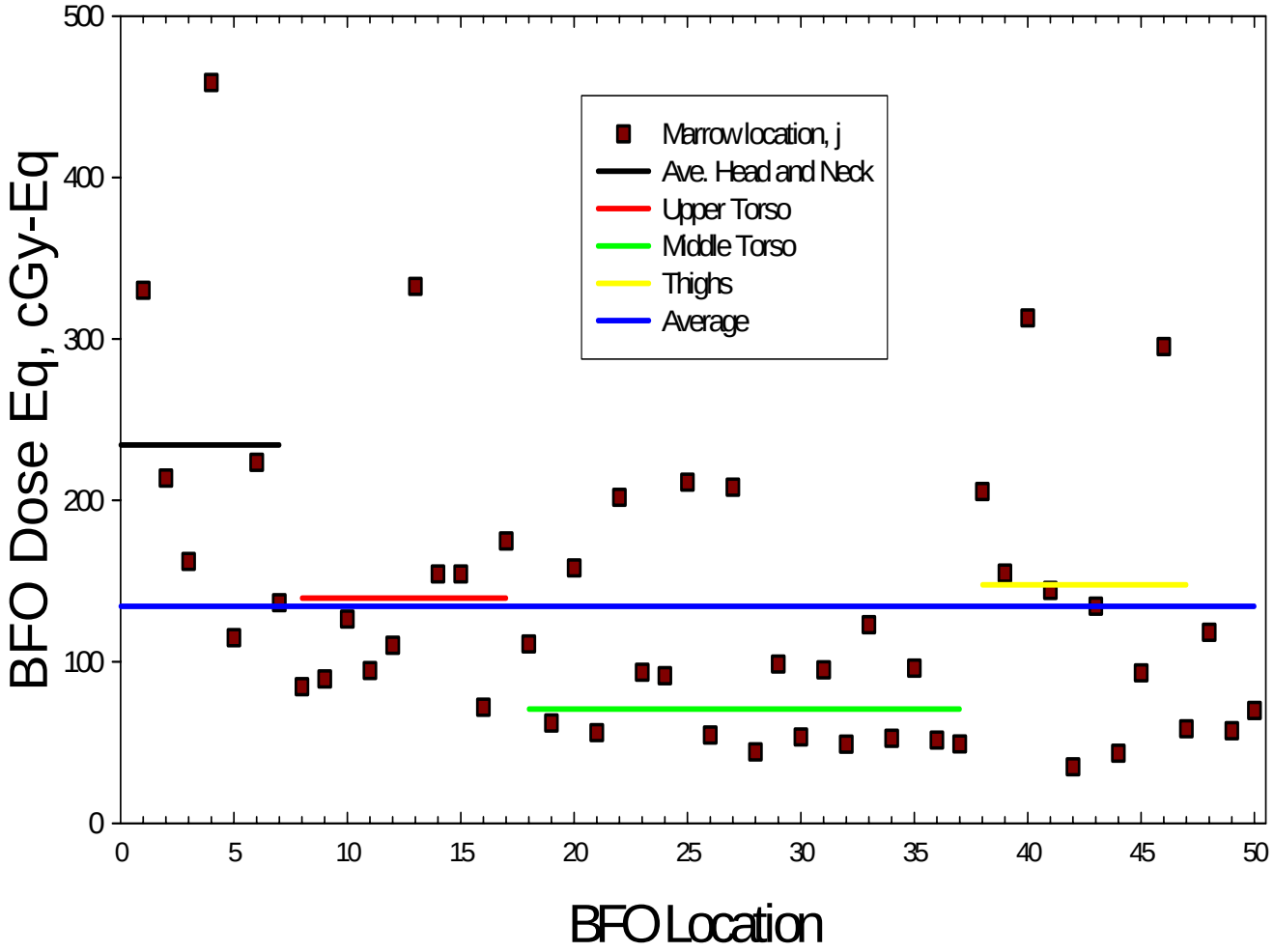


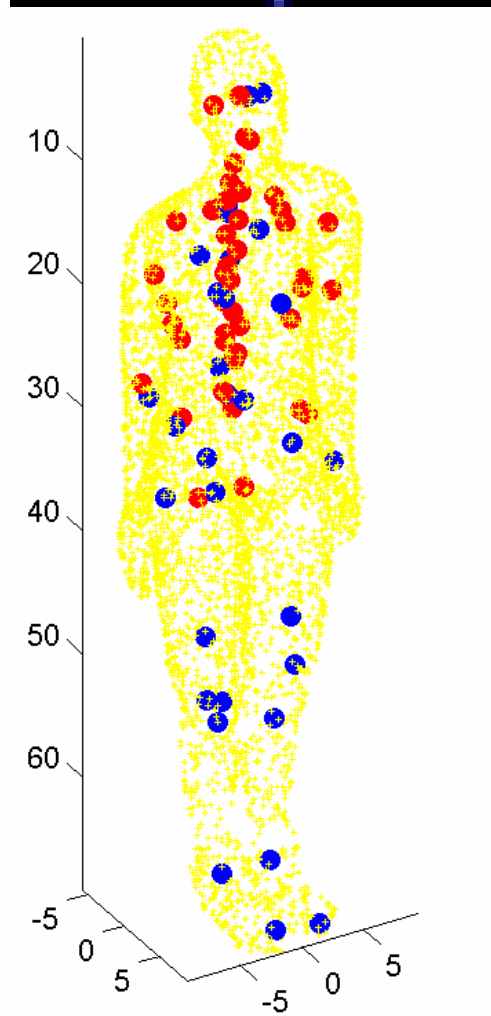
BFO Dose Rate
January 16-22, 2005 SPE



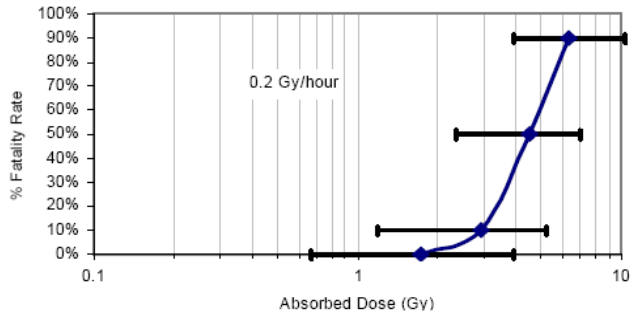
August 1972 Solar Proton Event

(1 g/cm^2 Al shielding)





Dose-Rate Dependence of LD_{50} for Uniform Exposures



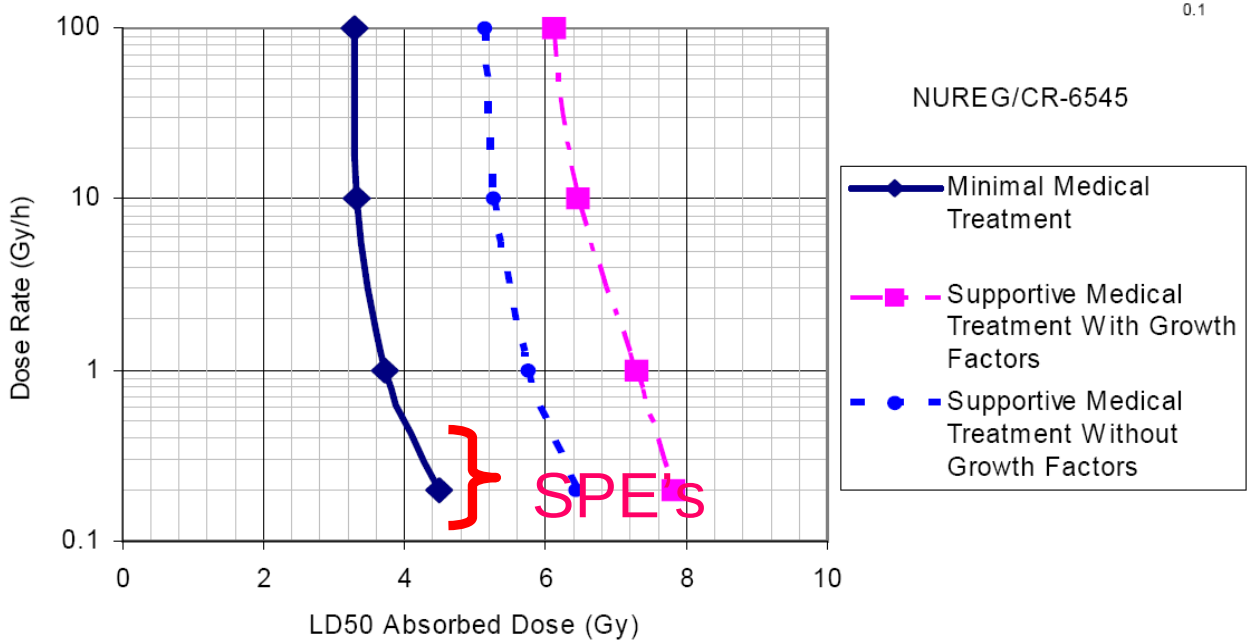


Figure 2. Effect of medical treatment and dose rate on the LD_{50} from gamma radiation (digitized data from Haskin et al. 1997)

SPE's Heterogeneous Dose Distribution Further Increases LD50

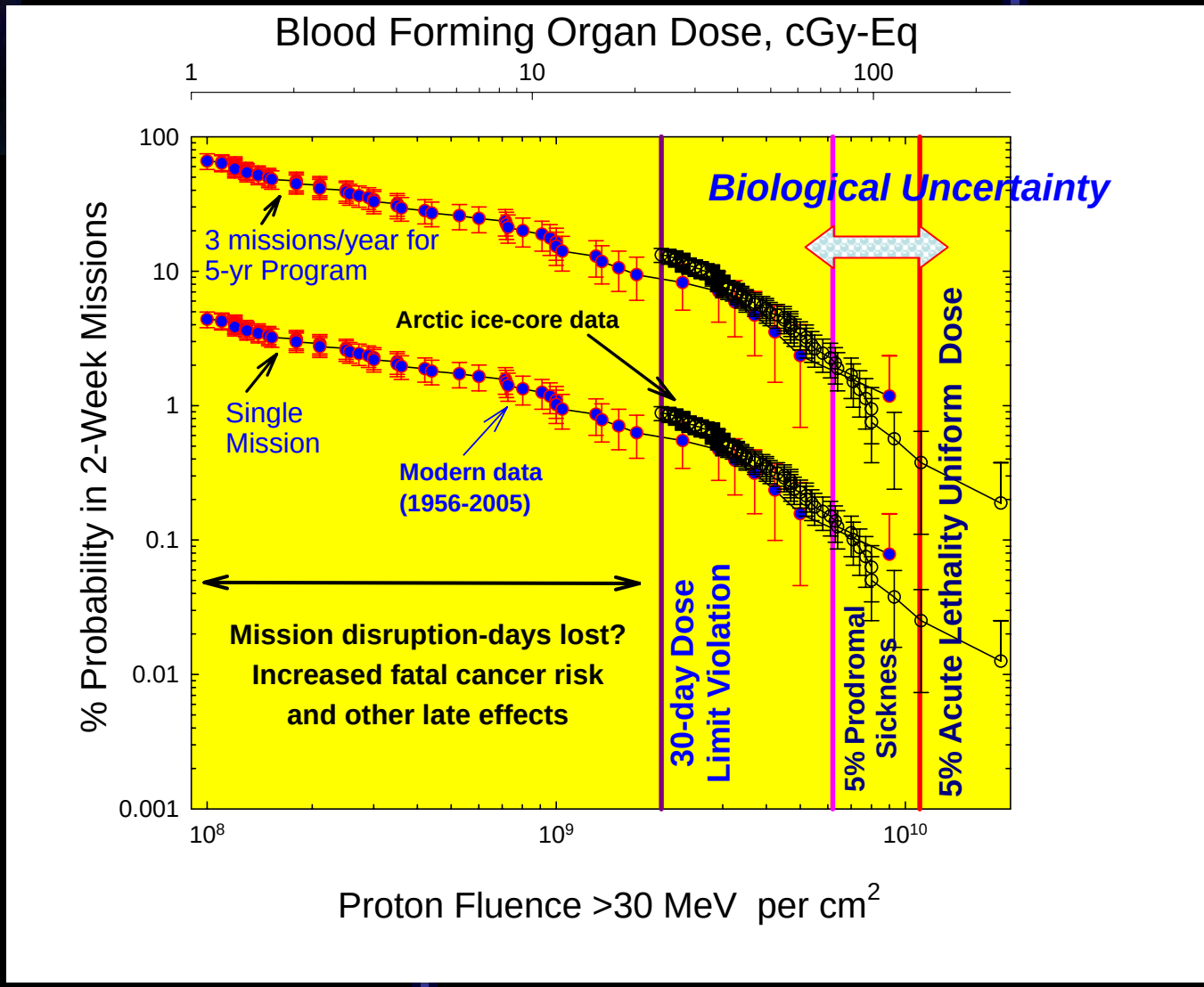
MODIFICATION OF LETHAL DOSE ACCORDING TO LATERALITY OF EXPOSURE*

Factor	Dog	Sheep	Pig
Body Mass (kg)	7-13	32-57	62 (average)
Radiation	X rays (1 MeV)	X rays (1 MeV)	X rays (2 MeV)
LD_{50} Mean ± SE	(Roentgen at midplane of exposure volume in absence of animal)		
Unilateral Exposure (UE)	386 ± 10	303 ± 13	434 ± 13
Bilateral Exposure(BE)	321 ± 9	252 ± 17	362 ± 13
Difference (UE-BE)	65	51	72
Ratio (UE/BE)	1.20	1.20	1.20

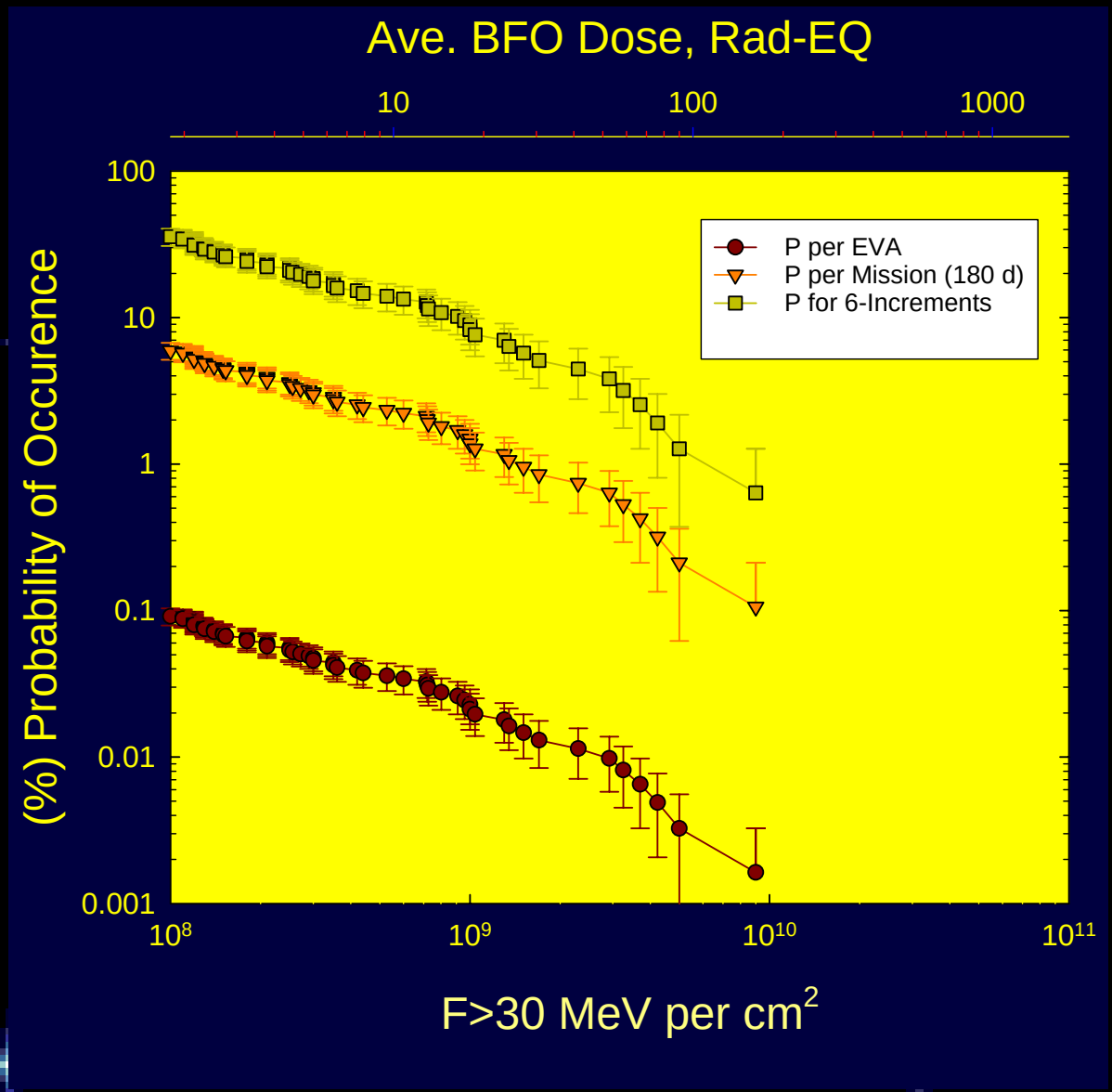
*A unilateral exposure from any radiation type may result in the sparing of distant stem-cell populations, thereby raising the LD_{50}.

Cerveney et al. Review

SPE Risks in Apollo Command Module

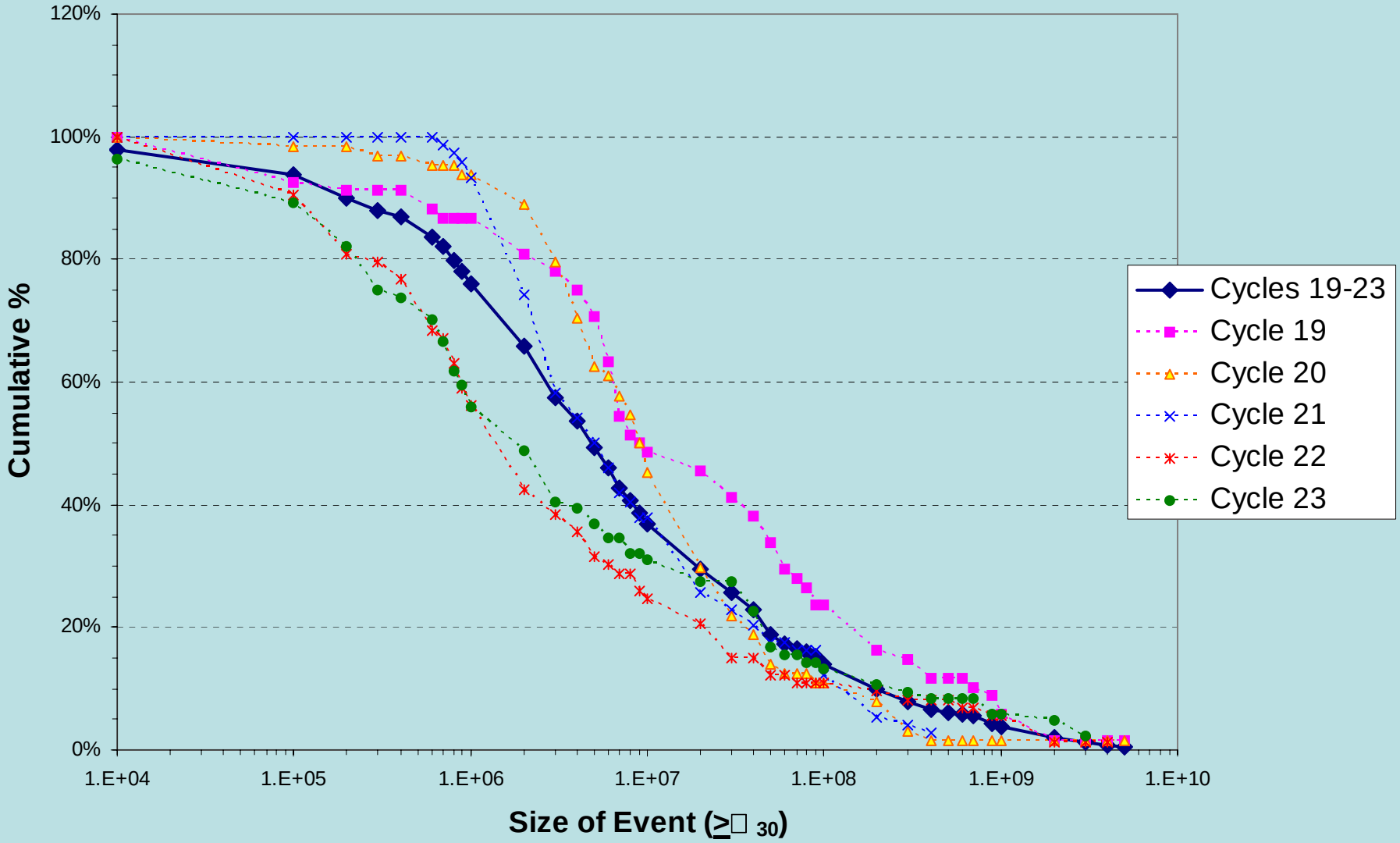


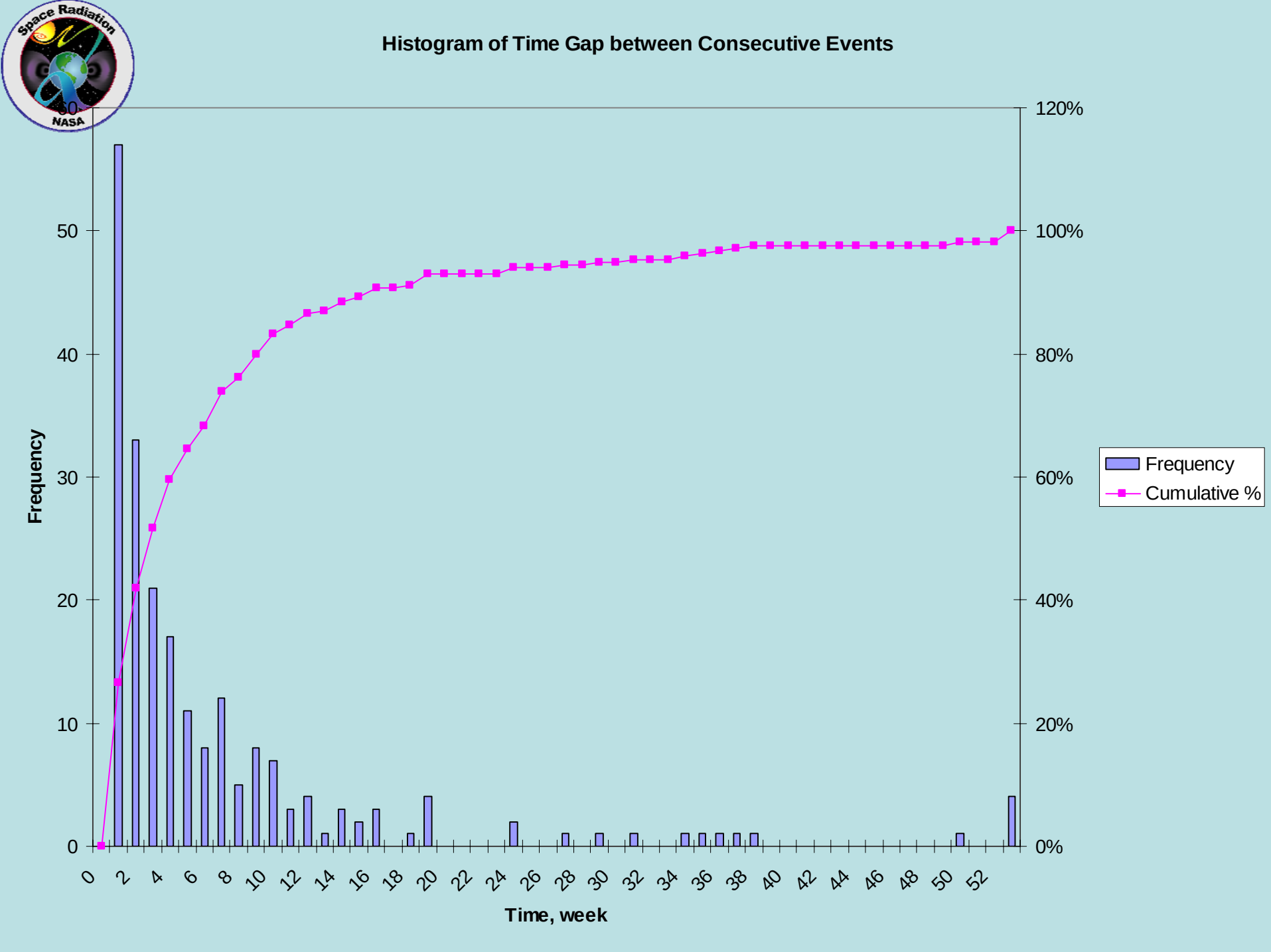
SPE Risks- Lunar Surface EVA's



- Assumptions
  - 7 hr EVA
  - 65 EVA's in 180-d surface stay
  - Multiple Outpost Increments
  - 3 hr EVA response time to shelter
  - $Pc=P_{SPE}xP_{Risk}$
- Issues
  - Lethality minor concern (Pc<1%)
  - Prodromal likely (Pc>10%) for NASA program

Cumulative Distribution of SPE

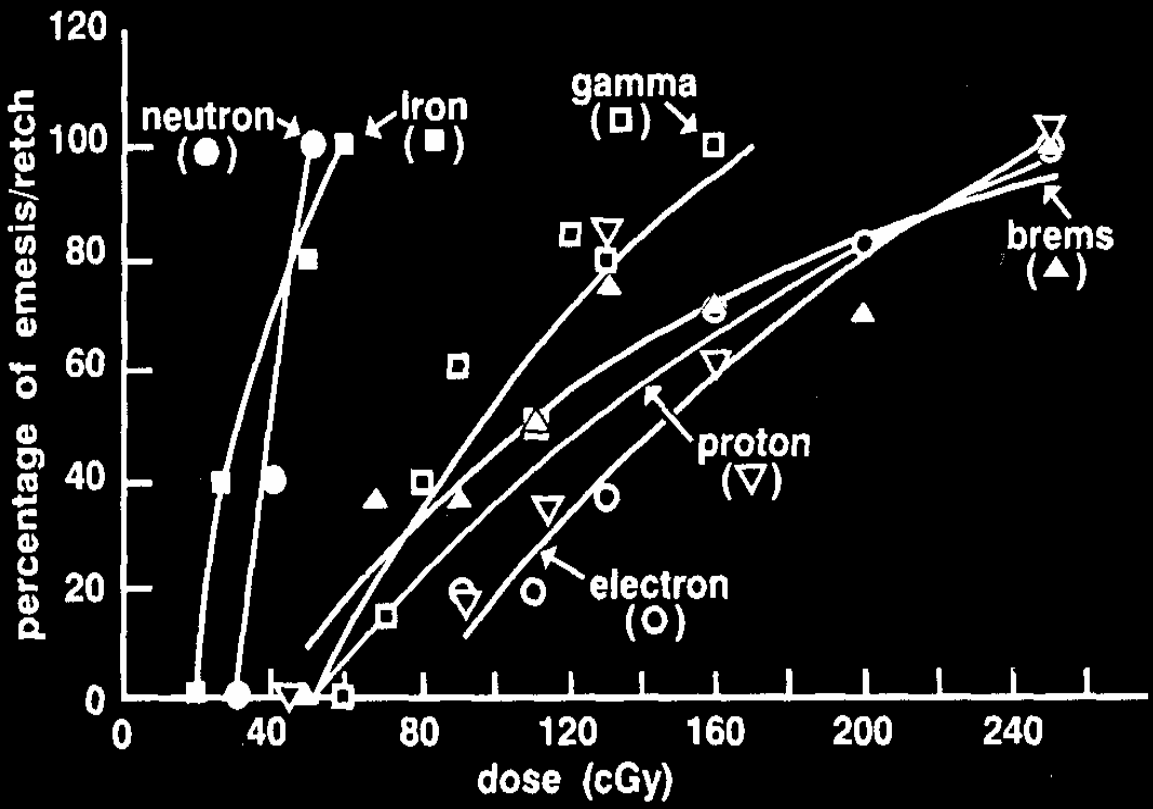



Histogram of Time Gap between Consecutive Events
Frequency
Time, week
Frequency
Cumulative %
0
10
20
30
40
50
60
0%
20%
40%
60%
80%
100%
120%
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
48
50
52

Acute Dose Responses and Thresholds

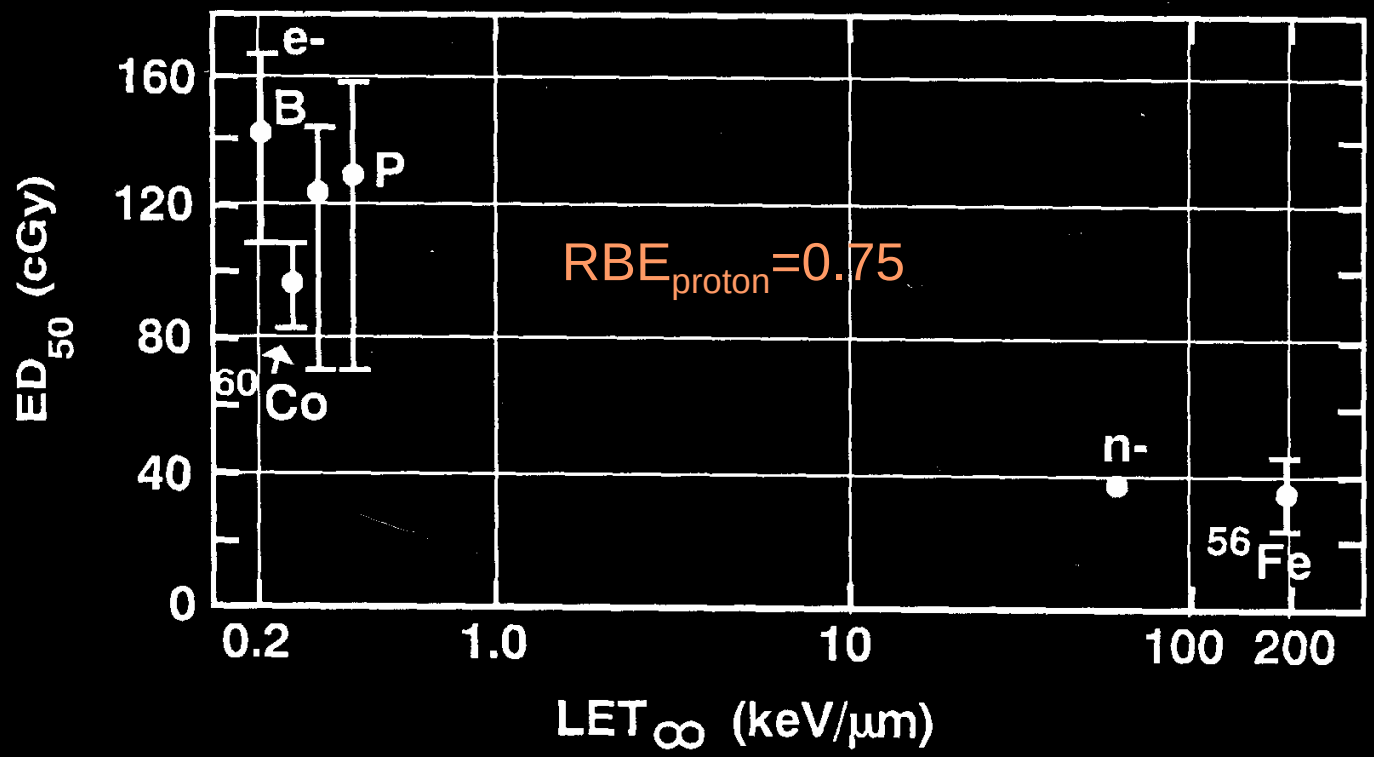
- Threshold dose dependencies
  - Acute risk (endpoint)
  - Dose-rate and radiation quality
  - Space flight stressors?
  - Individual sensitivity?
  - GCR background?
- Extrapolation to humans?
  - Shape from animal data
  - ED50 from Human studies

Rabin et al. (1994)
Retching/Emesis
in Ferrets



RBE's for Prodromal Effects

- High-energy Protons RBE<1
- Mixed-field protons RBE=1.1 used in Radiotherapy
- Paucity of data across acute risks to assess SPE RBEs



Rabin et al. (1994)
Retching/Emesis
in Ferrets

Potential Acute Risk CM's

- Because SPE doses are below ED50 for prodromal most effects will manifest after EVA is concluded
- Classes of Biological CM's of Interest
  - Antiemetics
    - **Neuroleptics (phenothiazines, butyrophenones)**
    - **Anticholinergics**
    - **Anthihistaminics H1 and H2**
    - **Cannabinoids**
  - Cytokines and Growth Factors
  - Antimicrobial therapy for infection control
  - Radioprotectors and anti-oxidants are generally not protective of prodromal effects
    - **Combinations with Antiemetics are of interest**
  - Anti-inflammatory drugs

Conclusions

- NASA Realignment around the Constellation Program shuffles research time-lines to place earlier emphasis on Acute Risk assessment and Biological CM Development from SPE's
- The risk of Acute Lethality from Major SPE is small due to cumulative dose, dose-rate, and dose distribution
- Major goals of a new NSBRI research team should be on Prodromal (Acute) Risk assessments and Countermeasure Development
- Risk questions include:
  - Dose-rate modifiers
  - Heterogeneous tissue doses
  - RBE effects

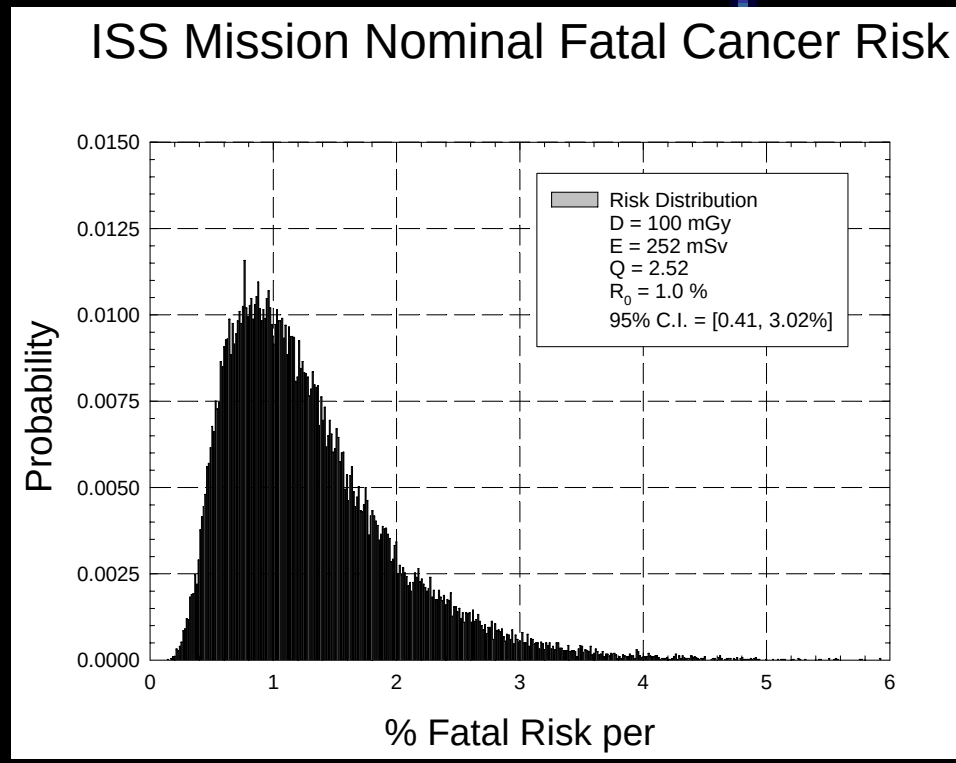
Conclusions- continued

- The risk of infection and immune suppression should be a major focus of new NSRBI Acute Radiation Risk Team
  - Synergistic effects with other flight stressors
- CM's post-exposure are most likely scenario
- Biological Countermeasures research can leverage on low CRL developments from
  - Radiation Therapy (protection of normal tissues)
  - Homeland Defense related bio-terrorism research

Backup material

NASA New Standards for Radiation Limits

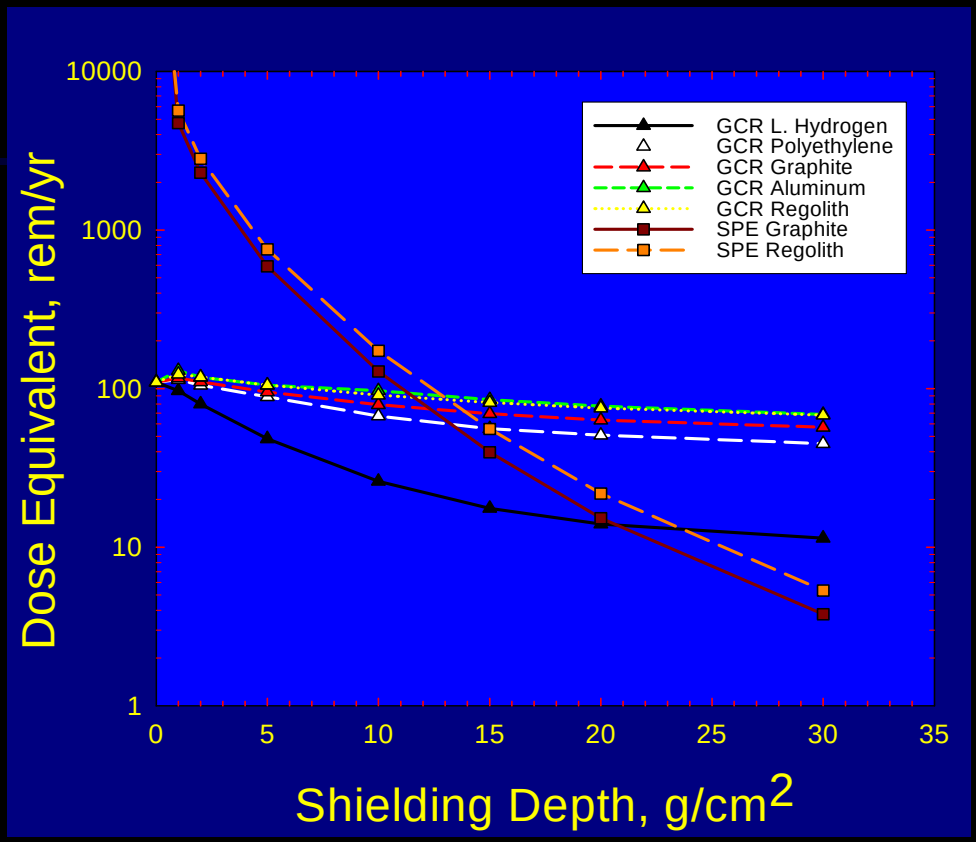
- NASA uses gender and age specific radiation limits
- Revised standard applies a 95% confidence level to the career limit of 3% risk of fatal cancer
- 95% confidence is conservative
  - **Specific risk probabilities of individuals**
  - **Narrows range of increased risk**
  - **Uncertainties-**
    - **Epidemiology data**
    - **Dose-rate effects**
    - **Radiation Quality (QF)**
    - **Dosimetry/transport codes**



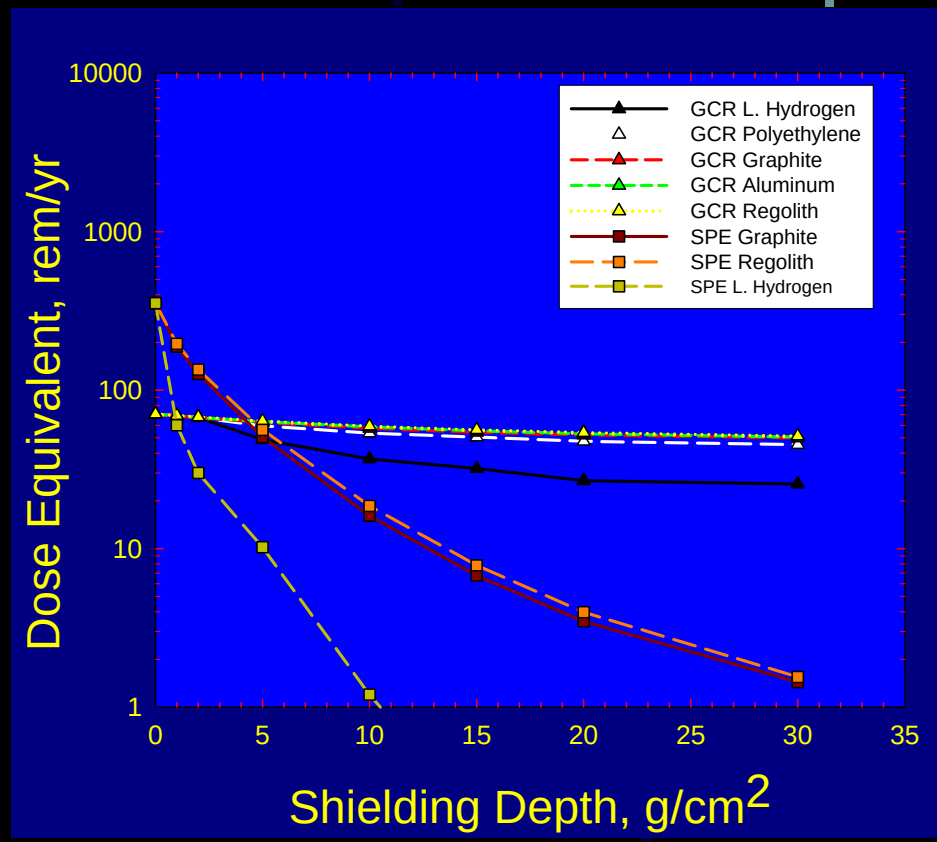
Monte-Carlo simulation of risk estimates Including range of quality factors, dose-rate Factors, epidemiology data, and errors in Dosimetry or transport codes.

Galactic and Solar Cosmic Rays
- Limitations of Radiation Shielding

No Tissue Shielding



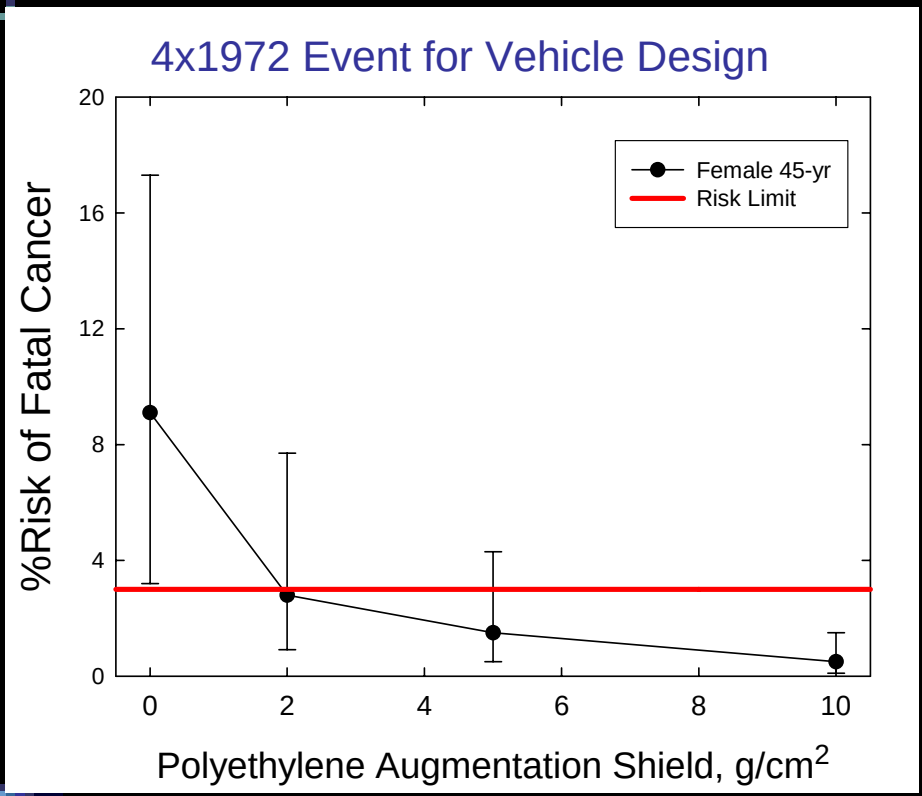
With Tissue Shielding

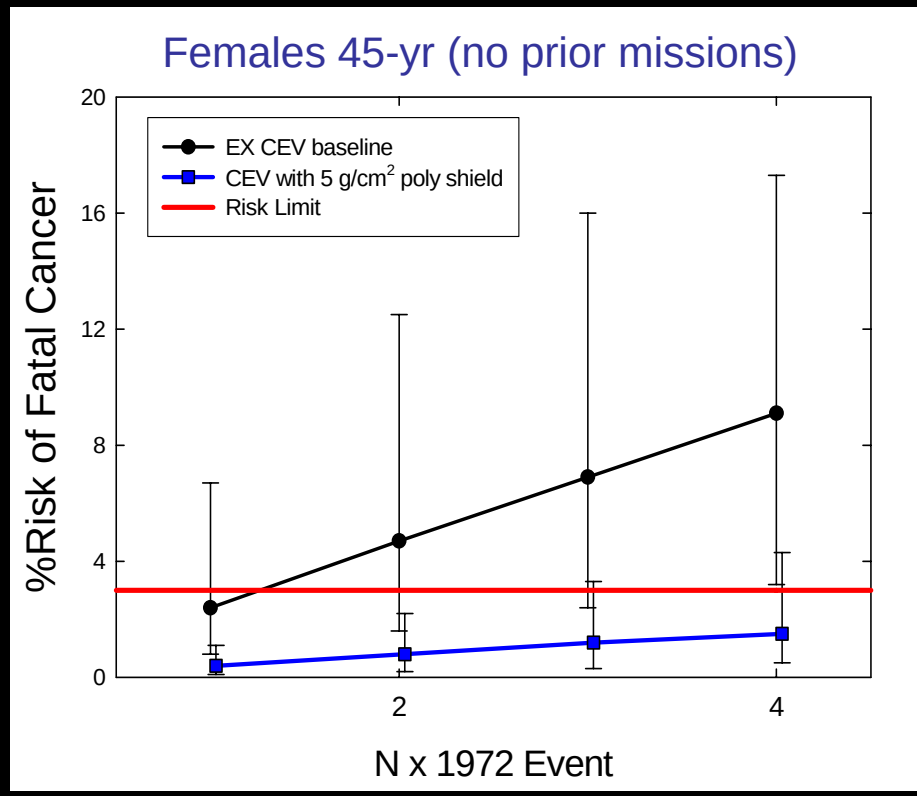


August 1972 SPE

Solar Proton Events

- What is the largest Solar proton event? Flux, Spectra, Dose-rate?
  - Statistical models of 99% worst-case events
  - Historical information from ice-core samples (14th to 19th centuries)
- Large SPE's will have variable dose-rates (1 to 50 cGy/hr) adding to uncertainties in DDREF





Accuracy of Physics Models: ± 20%
(environments, transport, shielding)

HZETRN Comparisons to GCR Secondary Energy Spectra on STS 48
- Because of Earth Magnetic Cutoff predominantly secondary protons and deuterons are measured (Stringent test of HZETRN Code)

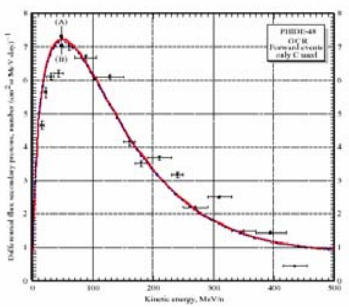


Figure 5. Comparison of observed and calculated secondary proton energy spectra.

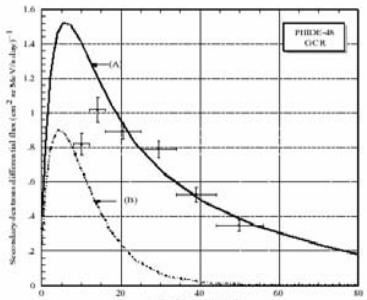


Figure 6. Comparison of observed and calculated secondary deuteron energy spectra.

Absolute Predictions from HZETRN and Flight Measurements

Mission	DATE	Inclination	Altitude	Shielding	Dose, mGy/d			Dose Eq., mSv/d		
					Measured	Theory	%Difference	Measured	Theory	%Difference
STS-40	1991	39	293	Dloc2	0.052	0.048	7.7	0.13	0.16	-23.1
STS-49	1992	28.5	358	Dloc2	0.05	0.048	4.0	0.127	0.155	-22.0
STS-51	1993	28.5	296	Payload Bay	0.044	0.048	-9.1	0.144	0.154	-6.9
STS-57	1993	57	298	Payload Bay	0.113	0.109	3.5	0.422	0.434	-2.8
STS-57	1993	57	298	DLOC-2	0.138	0.11	20.3	0.414	0.37	10.6
Mir-18	1995	51.6	390	P	0.142	0.141	0.7	0.461	0.526	-14.1
STS-81	1997	51.6	400	0-sphere	0.147	0.135	8.2	0.479	0.521	-8.8
STS-81	1997	51.6	400	Poly 3-in	0.138	0.138	0.0	0.441	0.400	9.3
STS-81	1997	51.6	400	Poly 5-in	0.129	0.118	8.5	0.316	0.368	-16.5
STS-81	1997	51.6	400	Poly 8-in	0.128	0.113	11.7	0.371	0.323	12.9
STS-81	1997	51.6	400	Poly 12-in	0.116	0.111	4.3	0.290	0.298	-2.8
STS-89	1998	51.6	393	0-sphere	0.176	0.148	15.8	0.561	0.614	-9.4
STS-89	1998	51.6	393	Al 3-in	0.167	0.159	4.8	0.445	0.488	-9.7
STS-89	1998	51.6	393	Al 7-in	0.149	0.161	-8.1	0.529	0.617	-16.6
STS-89	1998	51.6	393	Al 9-in	0.171	0.162	5.3	0.492	0.541	-10.0

ISS Mission

CALCULATIONS & % DIFFERENCES

	TRAPPED (mGy/day)	GCR (mGy/day)	TOTAL (mGy/day)		% DIFF. (C-M)/M
BRAIN	0.066	0.077	0.143		13.3
THYROID	0.072	0.077	0.148		9.4
HEART	0.061	0.077	0.138		6.6
STOMACH	0.057	0.077	0.133		5.5
COLON	0.056	0.076	0.131		2.5
LIVER	0.053	0.077	0.130		-4.0

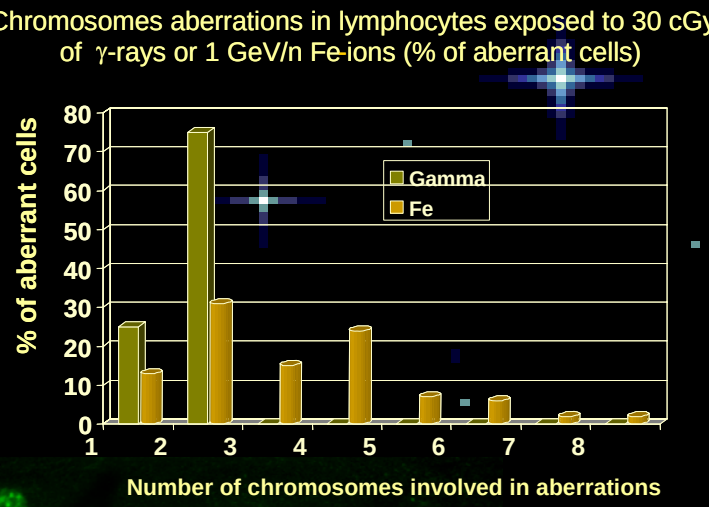
Phantom Data on STS-91 for Trapped + GCR (51.6 x 390 km)

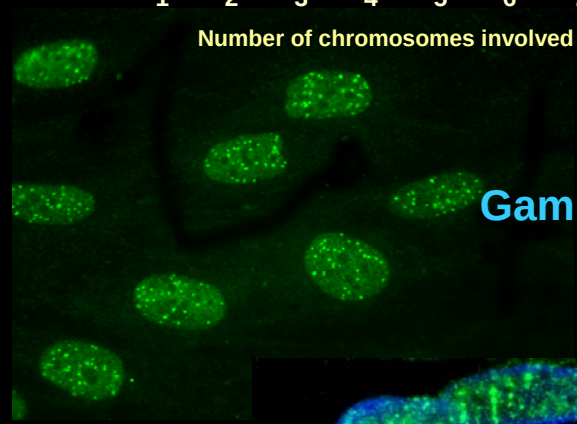
Organ	Measured (mGy)	Theory (mGy)	Theory* (mGy)	% Difference	% Difference*
Brain	2.23	2.42	2.26	-8.5	-1.4
Bone Surface	2.16	2.36	2.21	-9.3	-2.1
Esophagus	1.71	1.79	1.67	-4.7	2.2
Lung	1.92	1.81	1.69	5.7	11.9
Stomach	2.05	2.08	1.94	-1.5	5.2
Liver	1.88	2.15	2.01	-14.4	-6.9
Spinal Column	1.65	1.98	1.85	-20.0	-12.1
Bone Marrow	1.75	1.98	1.85	-13.1	-5.7
Colon	1.71	1.9	1.78	-11.1	-3.8
Bladder	1.58	1.87	1.75	-18.4	-10.6
Gonad	1.75	1.85	1.73	-5.7	1.2
Skin/Breast	2.46	2.58	2.41	-4.9	2.0
Skin/Abdomen	2.35	2.58	2.41	-9.8	-2.6

*Includes a correction to TLD efficiency vs. LET.

The Space Radiation Problem

- Space radiation is comprised of high-energy protons and heavy ions (HZE's) and secondary protons, neutrons, and heavy ions produced in shielding
  - Unique damage to biomolecules, cells, and tissues occurs from HZE ions
  - No human data to estimate risk
  - Animal models must be applied or developed to estimate cancer, CNS or other risks
  - Solar particle events (SPE) can not be predicted with sufficient warning at this time
  - Shielding has excessive costs and will not eliminate GCR
    - SPE's <u>can</u> be mitigated with shielding
    - GCR can not (energies too high)



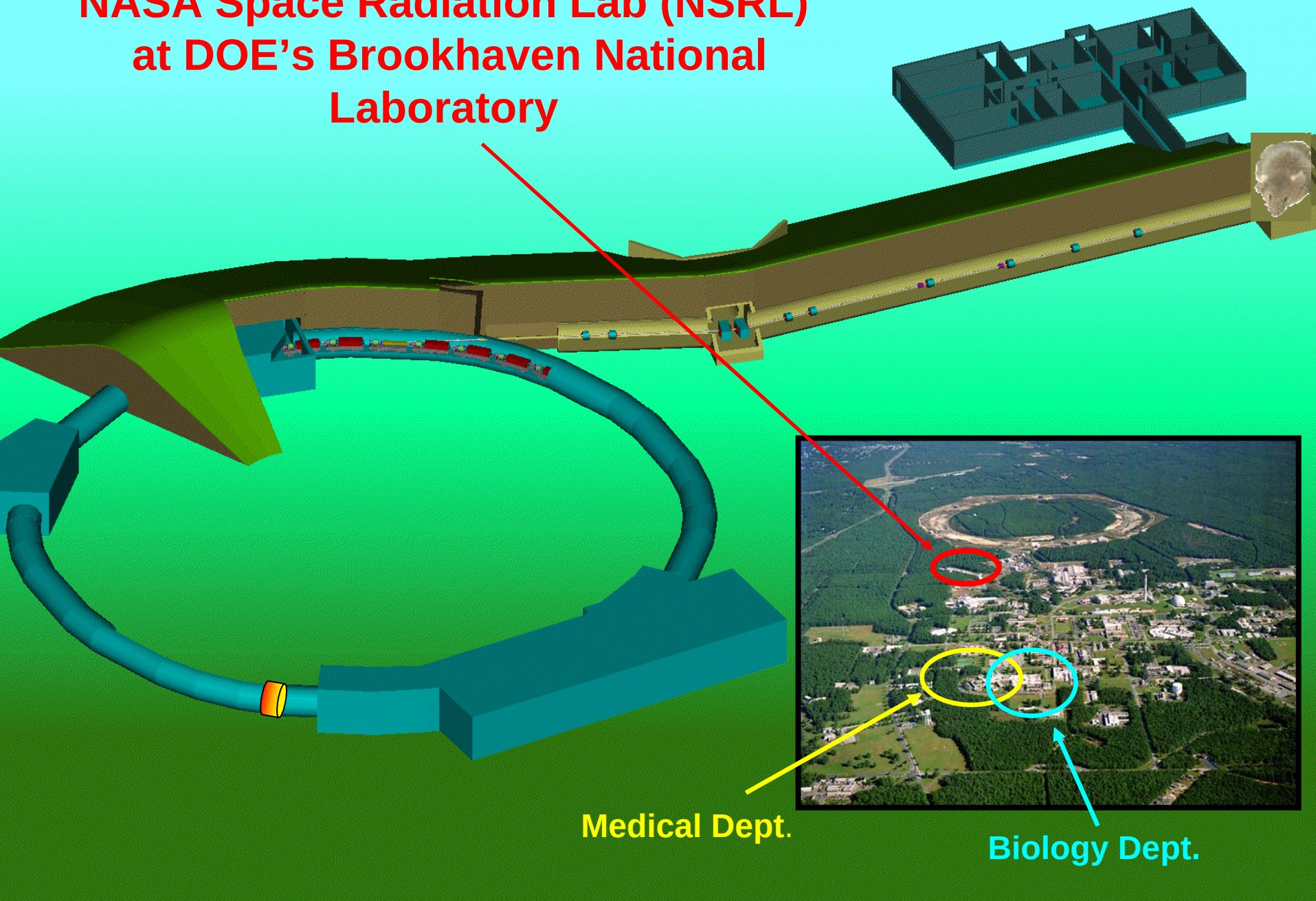


Gamma-rays

Clusters of γH2AX foci

Titanium

NASA Space Radiation Lab (NSRL) at DOE's Brookhaven National Laboratory



Medical Dept.

Biology Dept.