The Space Radiation Environment and Risk Mitigation with Medical Countermeasures

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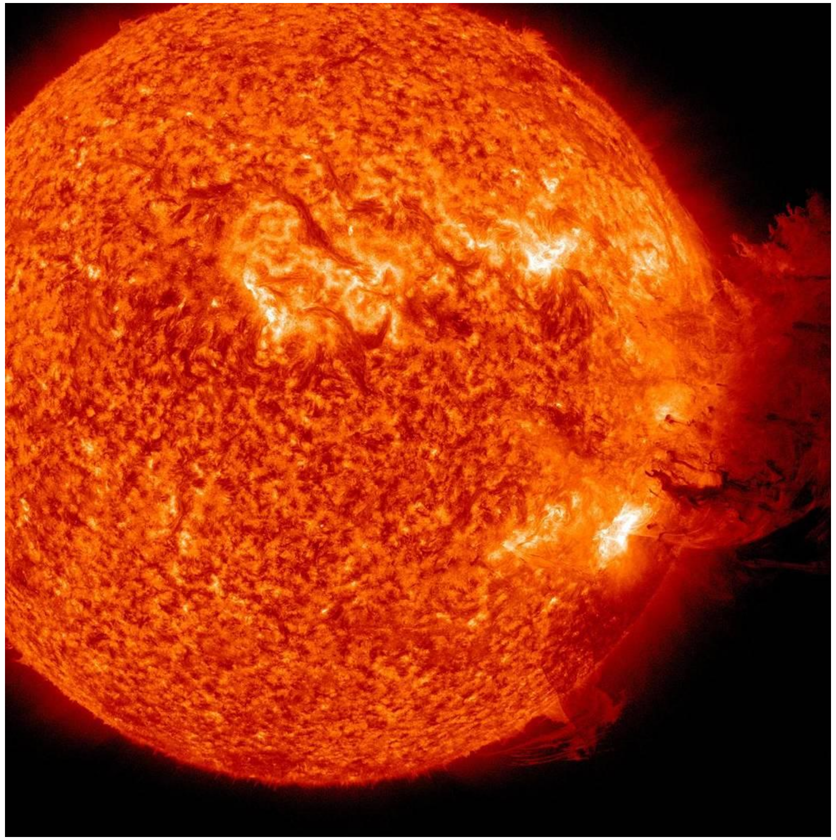
Image of Mars Courtesy of NASA

Overview

- Space radiation environment
- Radiation transport and exposure
- Space radiation risk challenges
- Typical terrestrial and space radiation exposures
- Potential health effects from space radiation
- Radiation risk mitigation strategies
- Investigation of medical countermeasures to mitigate risks
- Summary

Space Radiation Environment

Solar Particle Events (SPE)



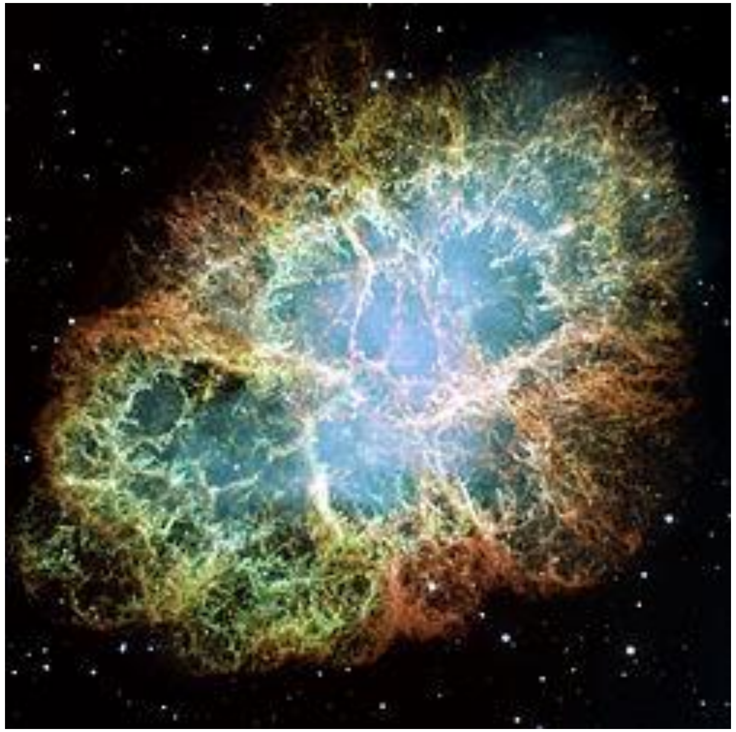
7 June 2011

Image Courtesy of NASA

- Consists of mostly protons with energies that range from fraction of MeV to several hundred MeV and higher
- Sporadic events
- More frequently occur near solar maximum
- Storm shelters can be constructed to minimize exposure risk

Space Radiation Environment

Galactic Cosmic Rays (GCR)



Crab Nebula

Image Courtesy of NASA

- Galactic Cosmic Rays originate from the shock waves of galactic supernovae
- Mostly composed of protons and heavier nuclei with energies that reach TeV/n (10^{12} eV/n) and higher
- Intensity near Earth depends on the solar cycle
- Difficult to shield from high energy and charge ions

Space Radiation Environment

Geomagnetically Trapped Radiation

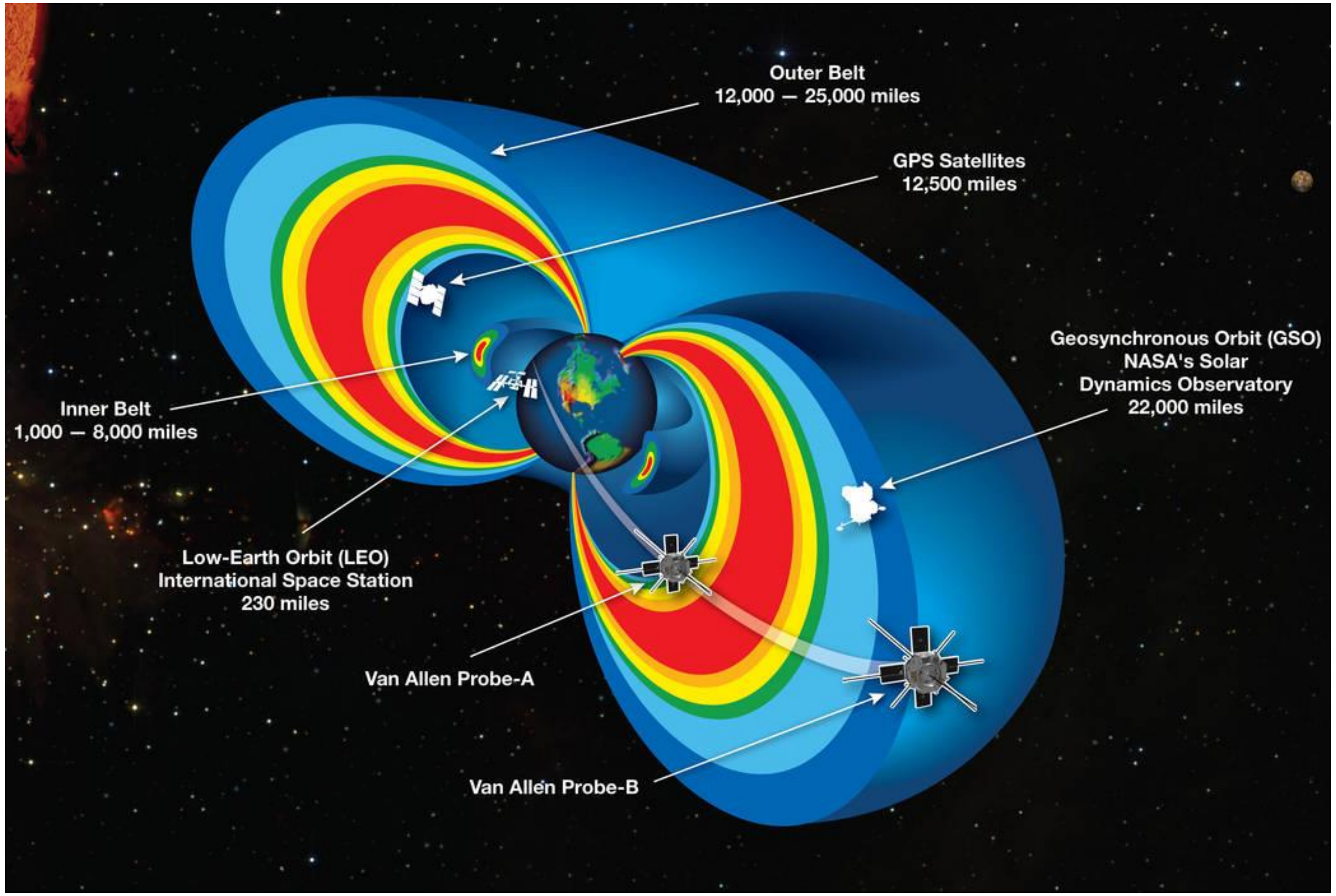


Image Courtesy of NASA

- Inner Belt: mostly protons and electrons
- Outer belts: composed of electrons
- Proton Energy < 250 MeV
- Electron Energy < 6 MeV

Vehicle and Radiation Transport

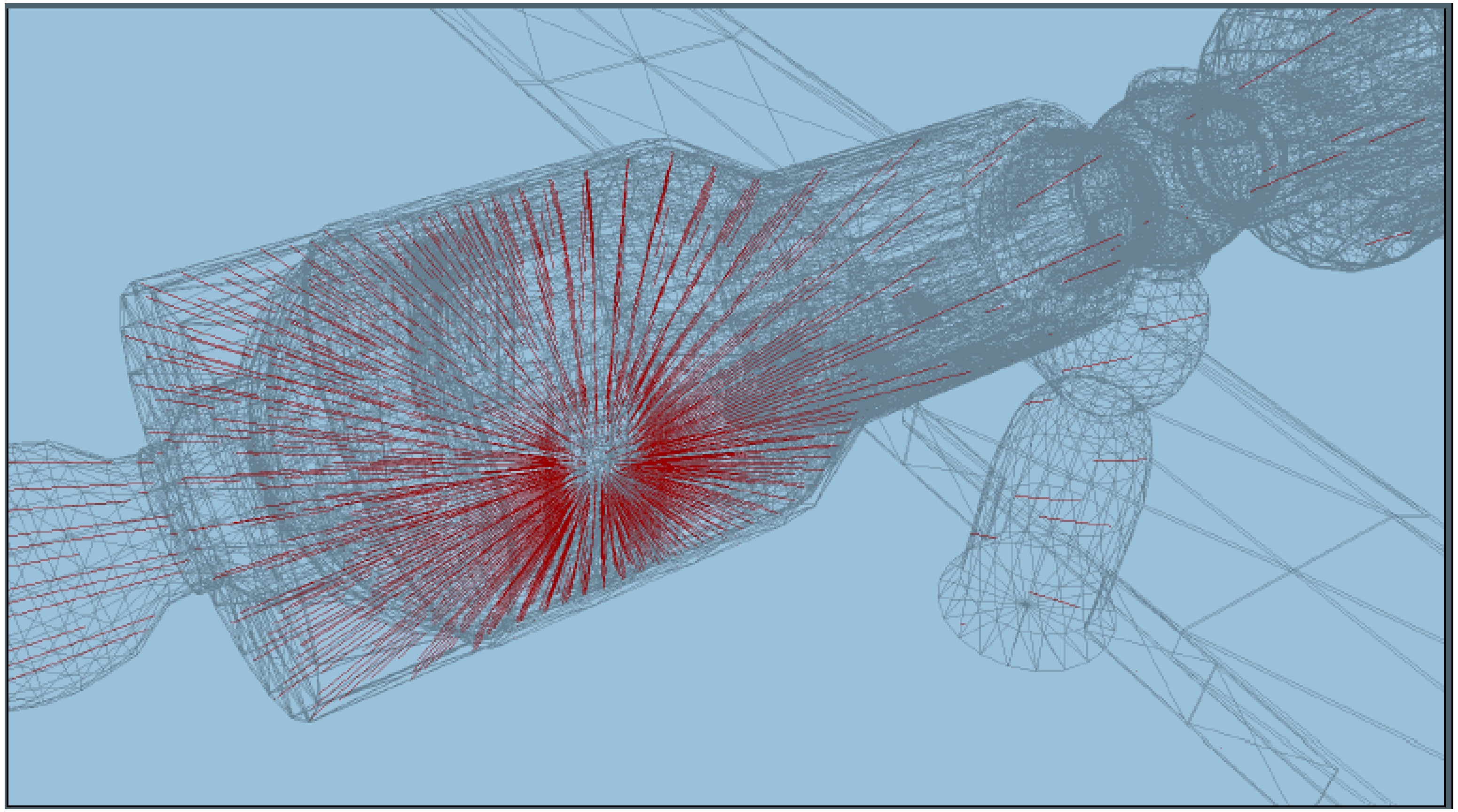
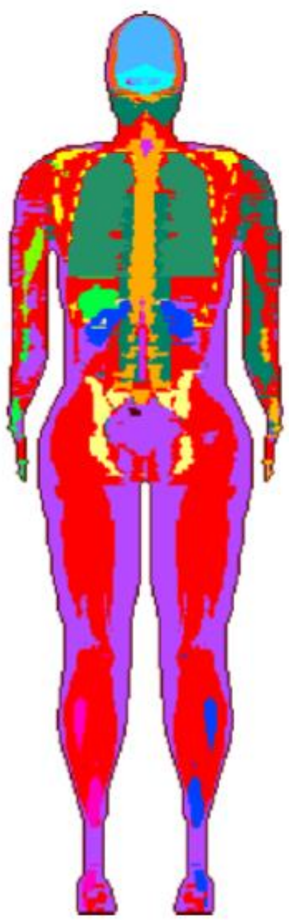


Image: Singleterry et al. *Acta Astronaut*. 68 (2011) 1086.
https://oltaris.nasa.gov

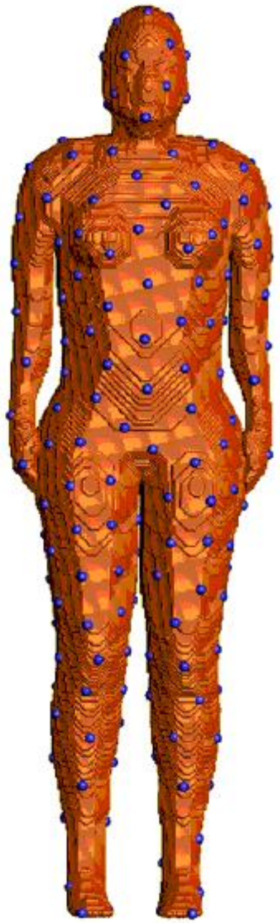
Radiation transport: given the flux (radiation environment) at the boundary of the vehicle, determine the flux inside some point in the vehicle

NASA uses the deterministic High Charge (Z) and Energy TRaNsport code (HZETRN).

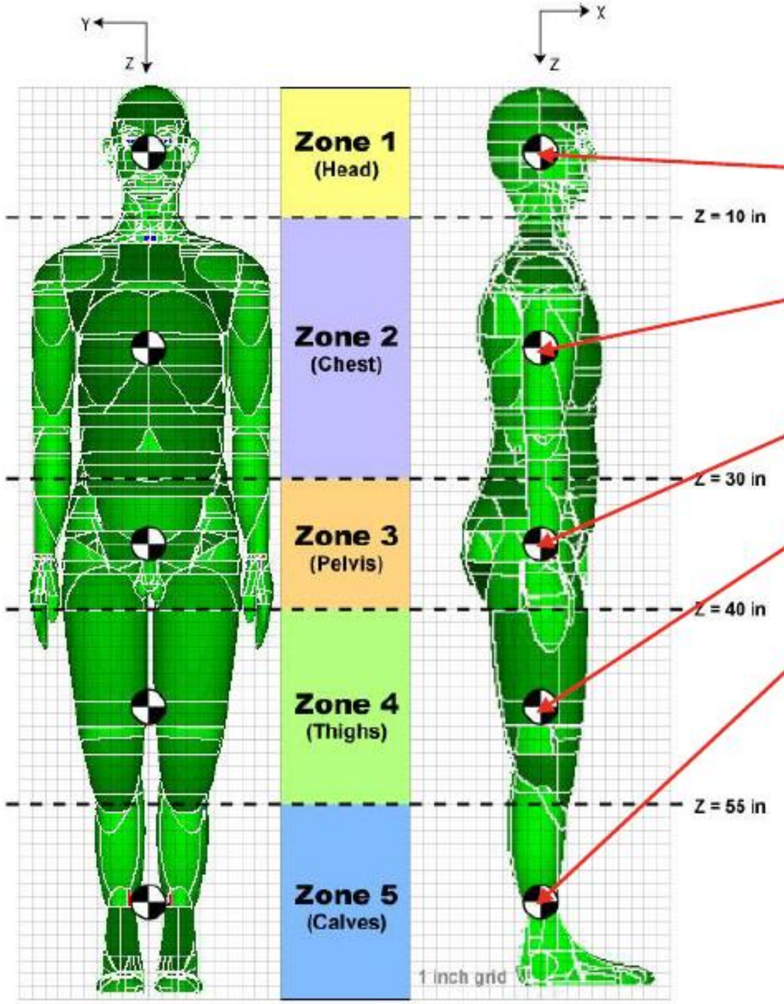
Human Phantom Models



Female Adult
voxel (FAX) Model



Skin Dose Points
in the FAX



Computerized Anatomical Man (CAM)

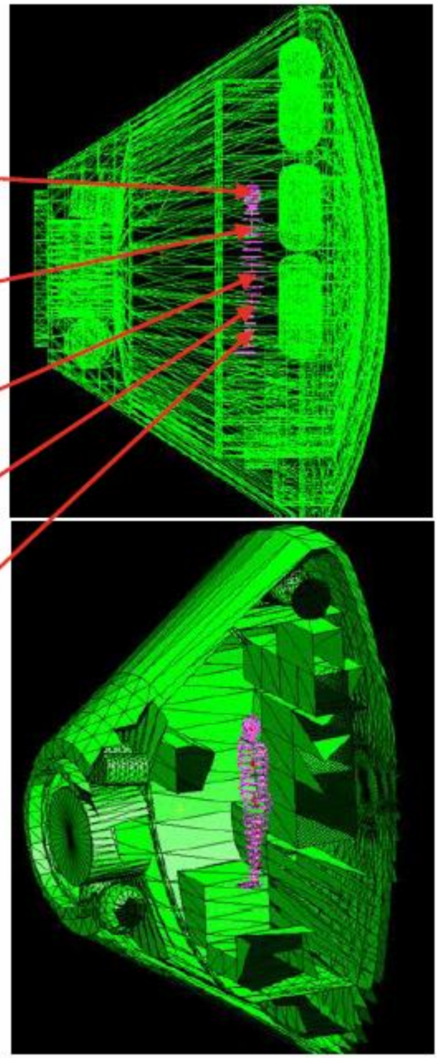
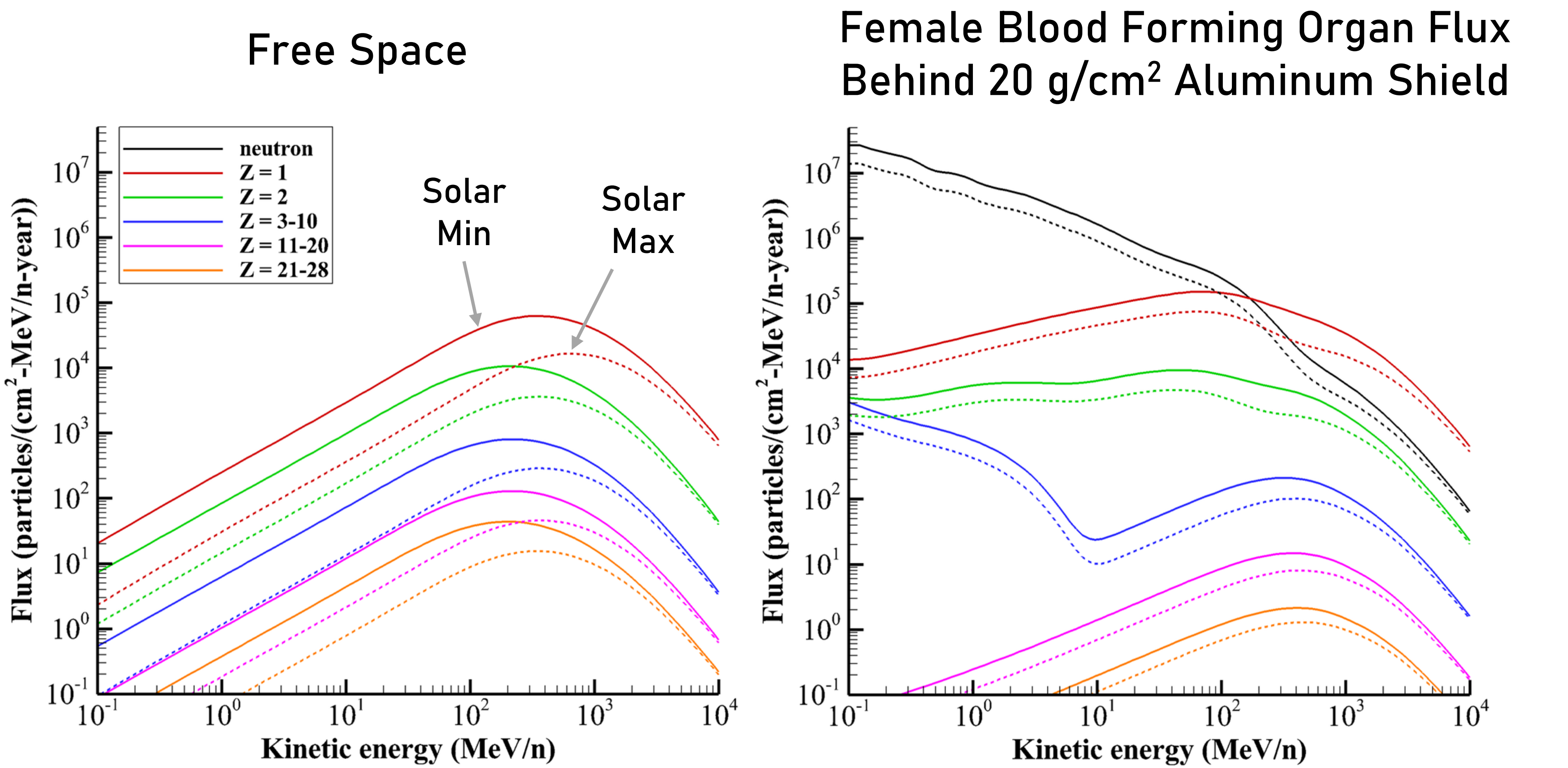


Image courtesy of NASA

GCR Flux



2010 Badhwar O'Neill GCR model

- **Solar Minimum: June 1976**
- **Solar Maximum: June 2001**

Simonsen et al. (2020). *PLoS Biol* 18(5): e3000669. https://doi.org/10.1371/journal.pbio.3000669

Space Radiation versus Low-LET Radiation

- Space radiation:
  - Complex of mixture of high-LET radiation
  - Delivered at low dose rates
  - Lack of human studies
- Low-LET radiation
  - Life span study (LSS) of the Japanese atomic bomb cohort
  - High dose and dose-rates of gamma rays
  - LSS evaluates excess cancer mortality and incidence from radiation exposure as a function of dose, sex, and age after radiation exposure

Linear Energy Transfer (LET) is the amount of energy that an ionizing particle transfers to a material traversed per unit length

DNA Damage to
Human Fibroblast Cells

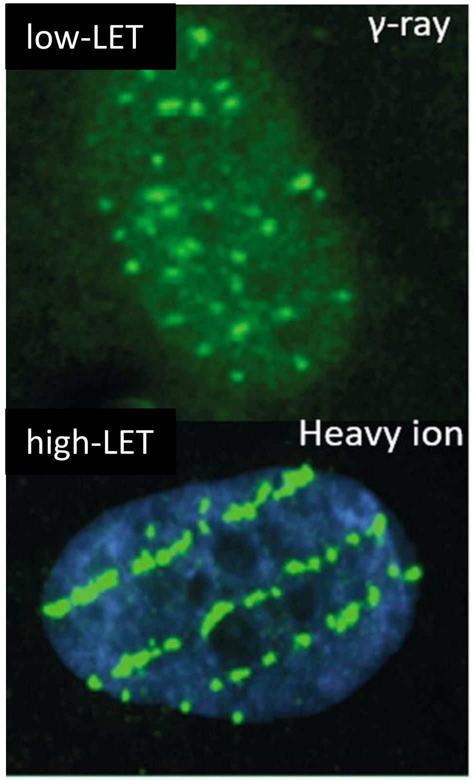


Image: Desai et al. *Radiat. Res*. 164 (2005) 518.

γH2AX foci (green) illuminate distinct patterns of DNA double-strand breaks in nuclei of human fibroblast cells

Translation to Space Radiation Exposure

- **Relative Biological Effectiveness (RBE):** ratio of the dose of the low-LET reference radiation to a dose of the radiation considered that gives the same biological effect
- Data from NASA Space Radiation Laboratory experiments are used to estimate RBE_m

Space Radiation Exposure = Low-LET models x RBE_m x Space Radiation Dose (high-LET)

Models are a scaled down by DDREF

Dose and Dose-Rate Reduction factor (DDREF)

Translation to Space Radiation Exposure

- **Radiation quality factor (Q) is constructed from $\mathbf{RBE_m}$**
- NASA Q
  - Consists of densely ionizing and sparsely ionizing components

Space Radiation Exposure = Low-LET models x Radiation Quality Factor (Q) x Space Radiation Dose (high-LET)

Models are a scaled down by DDREF

Dose and Dose-Rate Reduction factor (DDREF)

Exposure and Permissible Exposure Limit

- **Dose Equivalent (H)**
  - Dose scaled by radiation quality factor (Q)
  - Example Units: (mSv/year)
- **Effective Dose:**
  - Weighted sum of tissue average dose equivalent
  - Tissue weights: radiosensitivity of specific tissues
  - Example Units: (mSv/year)
- **NASA Permissible Exposure Limit (PEL):**
  - Exposure should not exceed effective dose of 600 mSv
  - Corresponds to mean Risk of Exposure Induced Death (REID) for cancer mortality of 3% as estimated with the NASA space cancer risk model

Terrestrial Exposures

Exposure Scenario	Dose (mGy)
Chest x-ray	0.1-0.23
Computed tomography-Chest	20-30
Computed tomography-Full body	50-100
Cardiac catheterization	12-40
Mammogram	0.6-2.9

Cancer Radiotherapy to tumor: doses ≥ 20 Gy

Department of Energy Ionizing Radiation Dose Ranges Charge (2017)

Space Radiation Exposures

Exploration Mission	Mission Duration	Dose (mGy)	Dose Equivalent (mSv)[a]
ISS in LEO	6 months	30-60	50-100
ISS in LEO	1 year	60-120	100-200
Sortie to Gateway (free space)	30 days	20	55
Lunar surface mission (2 weeks on surface)	42 days	25	70
Sustained lunar operations	1 year	100-120	300-400
Deep space	1 year	175-220	500-650
Mars mission	650 to 920 days	300-450	870-1200

[a]Both NASA defined quality factors and ICRP 60 quality factors considered in range of estimates

Simonsen LC, Slaba TC, Guida P, Rusek A (2020) NASA's first ground-based Galactic Cosmic Ray Simulator: Enabling a new era in space radiobiology research. *PLoS Biol* 18(5): e3000669. https://doi.org/10.1371/journal.pbio.3000669

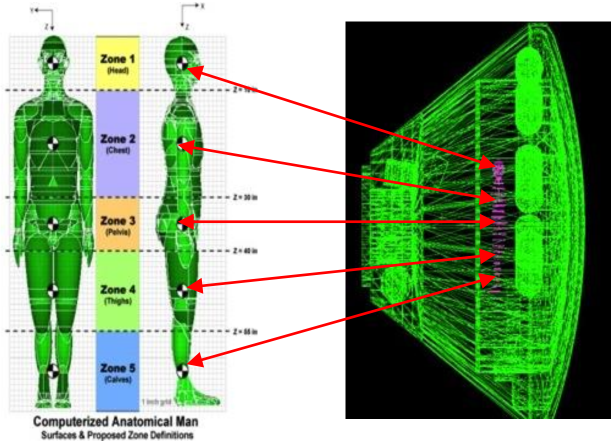
Space Radiation Health Risks

- **Risk of radiation carcinogenesis**
  - Morbidity and mortality risks
- **Risk of acute and late central nervous system (CNS) effects**
  - Changes in motor function and behavior or neurological disorders
- **Circulatory diseases**
  - Heart and Vasculature
- **Risk of acute radiation syndromes**
  - Prodromal effects (nausea, vomiting, anorexia, and fatigue), skin injury, and depletion of blood forming organs

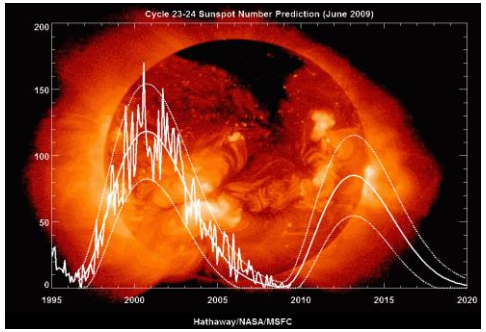
Mitigation Approaches

- Radiation shielding
- Mission planning: time in solar cycle and mission duration
- Crew selection: age, previous exposure
- Biomarkers predictive of radiation induced diseases
- Physical activity: studies indicate reduced cancer incidence

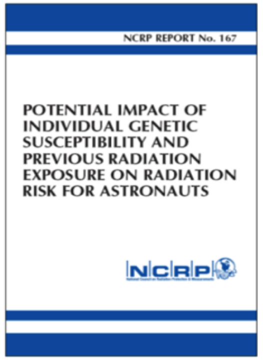
Shield Design and Optimization



Variations in Solar Activity



Individual Susceptibility


NCRP REPORT No. 167

POTENTIAL IMPACT OF INDIVIDUAL GENETIC SUSCEPTIBILITY AND PREVIOUS RADIATION EXPOSURE ON RADIATION RISK FOR ASTRONAUTS

NCRP

Exercise and Conditioning

Medical Countermeasures for Risk Mitigation

- Even with careful mission planning, optimum shielding and crew selection, etc., career radiation exposure limits are likely to be exceeded for many Mars mission scenarios

- Consequently, NASA is investigating the use of medical/biological countermeasures (MCMs) as an additional approach to reduce radiation risks

- Well-known drugs such as aspirin[a] and warfarin sodium[b] have been associated with lower cancer incidence and mortality

[a] Rothwell et al. *Lancet* **377**:31-41; 2011.
[b] Haaland et al. *JAMA Intern Med* **177**:1774-1780; 2017

Aspirin and Warfarin Sodium

- Aspirin
  - Rothwell et al. *Lancet* **377** (2011) 31.
  - Reduction of colorectal cancer mortality and incidence
  - **HR = 0.60 [0.45, 0.81]**
- Warfarin Sodium
  - Haaland et al. *JAMA Intern. Med.* **177** (2017) 1774.
  - Reduction of cancer incidence rate ratios:

Tissue	Incidence Rate Ratio
Stomach	**0.77 [0.65, 0.90]**
Prostate	**0.69 [0.65, 0.72]**
Bladder	**0.82 [0.75, 0.90]**
Brain	**0.74 [0.64, 0.87]**
Lungs	**0.80 [0.75, 0.86]**

Risk of Exposure Induced Death (REID)

$$\mathrm{REID}_T = \int_{a_E}^{a_{\max}} \lambda_T^M(a, a_E, \nu_T, H_T, \Delta_T) S_0(a|a_E) e^{-\sum_{T'} \int_{a_E}^{a} \lambda_{T'}^M(t, a_E, \nu_{T'}, H_{T'}, \Delta_{T'}) dt} da$$

$$\lambda_T = \nu_T \mathrm{ERR}_T \lambda_{0,T} + R_T^M(a)(1-\nu_T)\mathrm{EAR}_T$$

Conditional probability of survival for background population (no excess radiation exposure)

Competing causes of death due to radiation exposure

Background cancer mortality rates

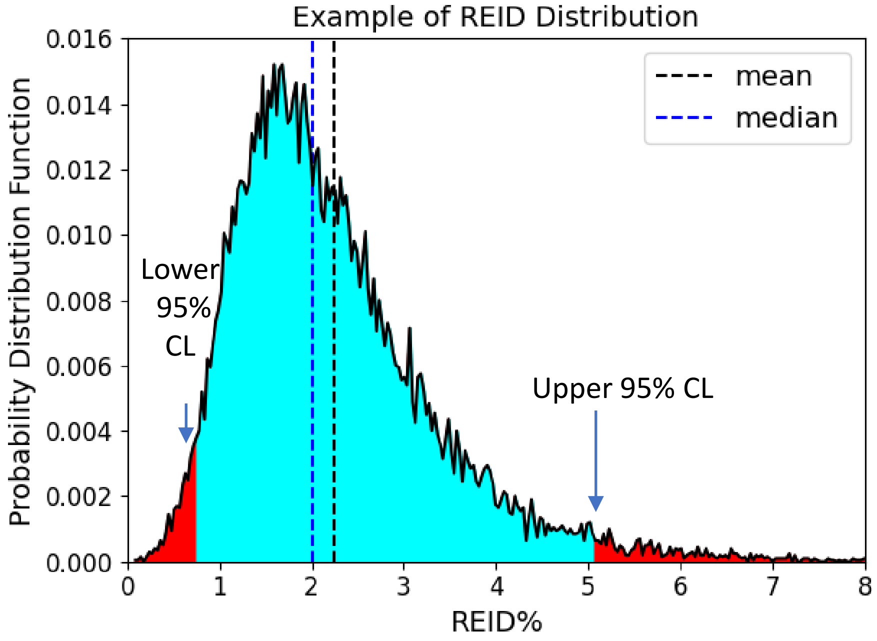
ERR = Excess Relative Risk
EAR = Excess Absolute Risk

Δ_T = Dose and Dose-Rate Effectiveness Factor

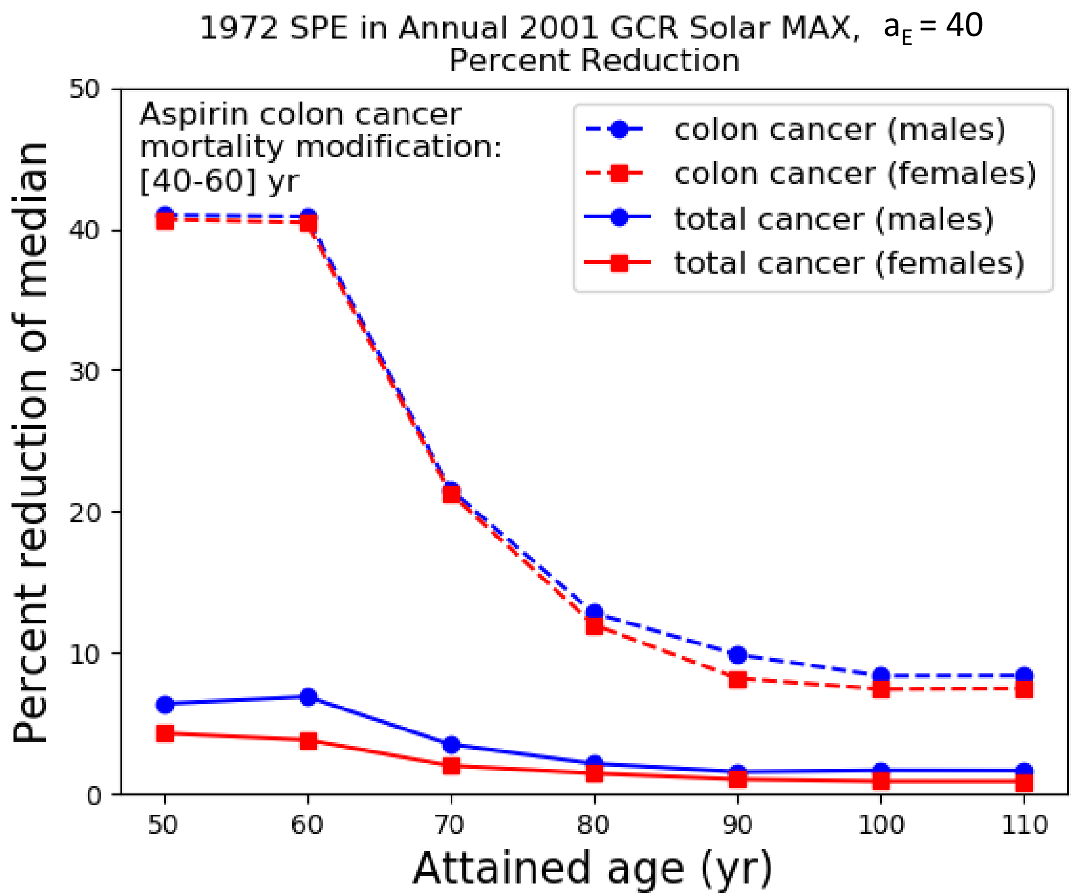
Tissue Dose Equivalent

$$H_T = \frac{1}{\rho}\frac{10^8}{6.24}\sum_A \sum_Z \int \phi_T(E, A, Z) LQ dE$$

Radiation Quality Factor



MCM Risk Reduction (1-yr deep space mission)

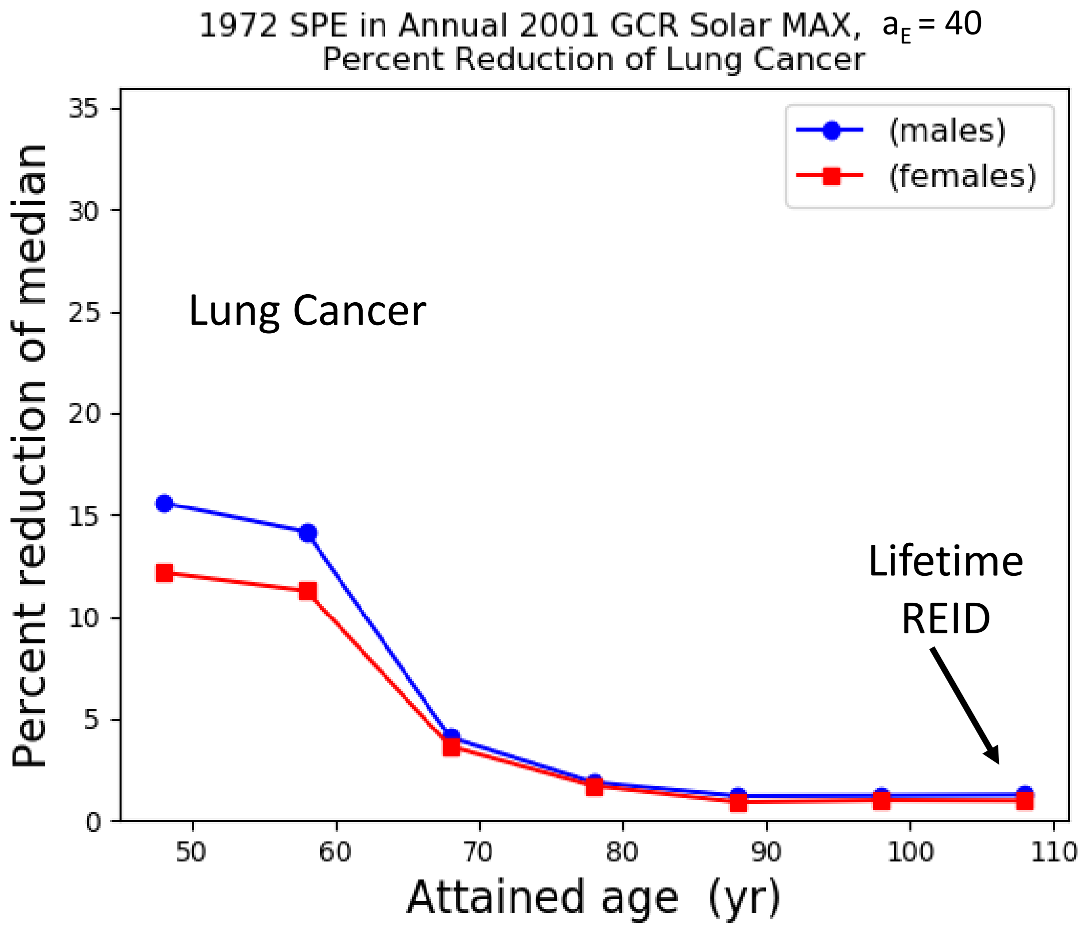


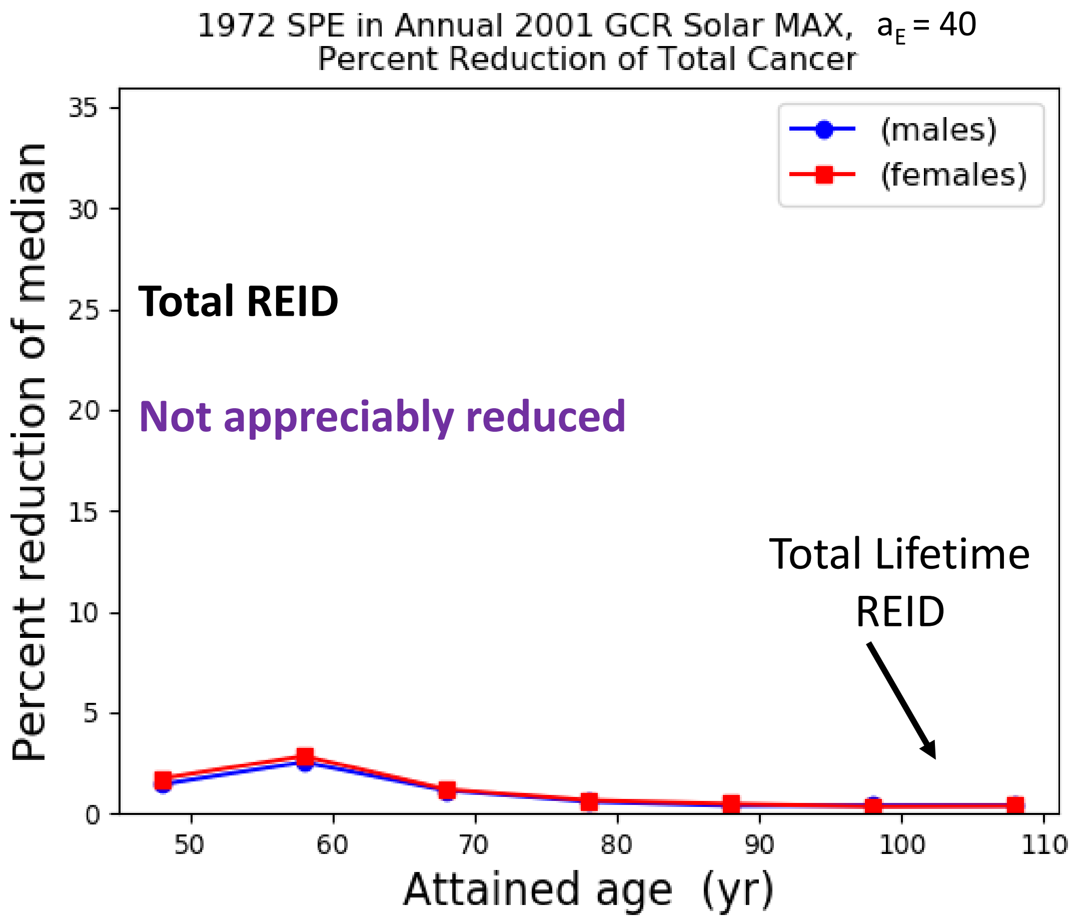
- Large reduction of REID% for colon cancer
- Total Lifetime REID% (associated with PELs) is not reduced appreciably
- NOTE: Results are highly sensitive to the assumptions of the study

Werneth et al. *Life Sci. Space Res.* 25 (2020) 71.

MCM Risk Reduction (1-yr deep space mission)

- **Warfarin sodium study**



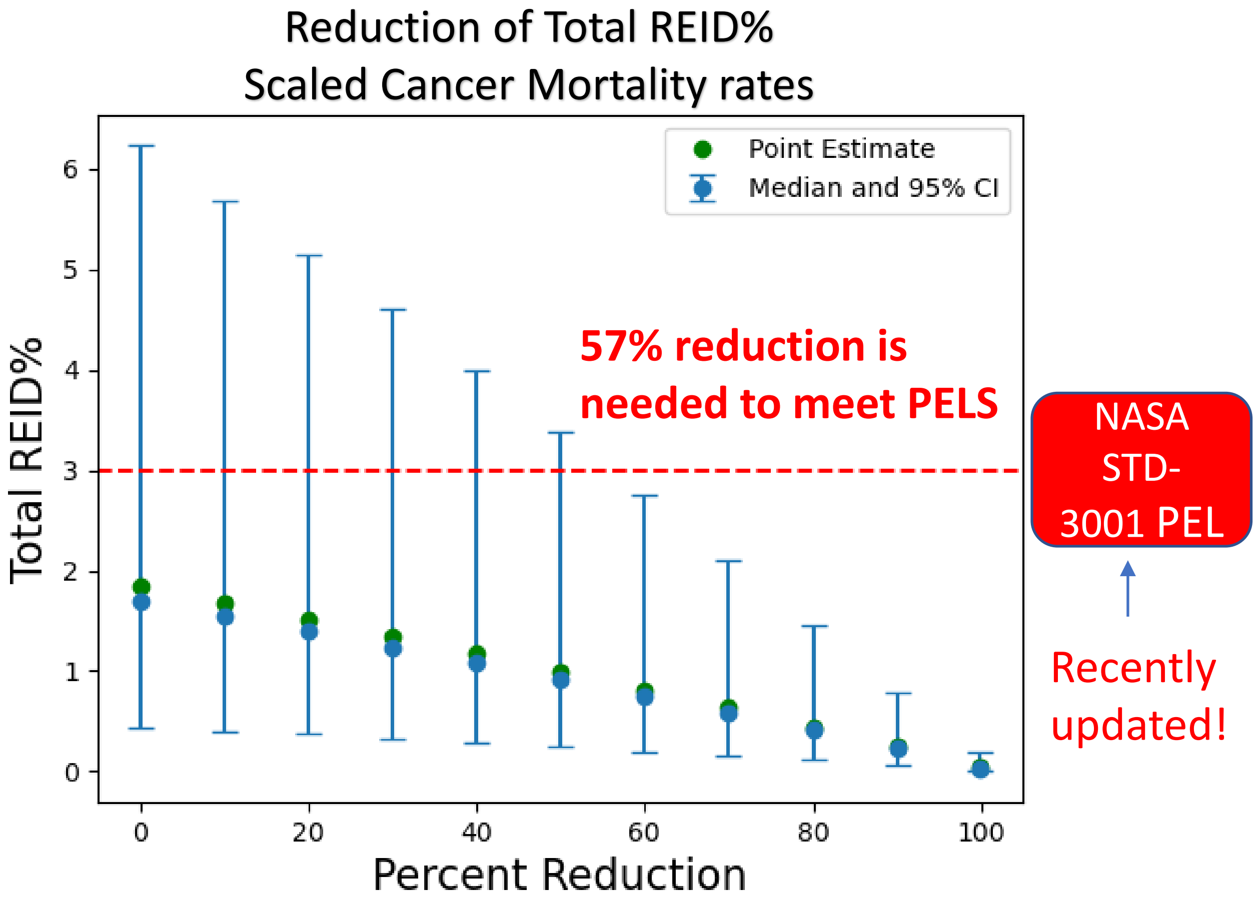


Werneth et al. *Life Sci. Space Res.* 25 (2020) 71.

MCM Reduction Needed to Meet PELs

- **What MCM reduction requirements are need to meet NASA PELs?**
- Mars mission scenario
  - 2001 GCR at solar max., August 1972 SPE, 20 g/cm^2 aluminum shield,
  - Mars design reference mission: 21 months of transit, 1 month stay on Martian surface (very short mission)
  - 45 yr-old female
- Sensitivity analysis assumptions
  - There exists a single MCM that can reduce all cancer mortality
  - MCM will act from age of radiation exposure until end of life

MCM Reductions Needed to Meet PELs



- Based on these results, PELs are not likely achieved with MCM alone
- MCM should be considered as part of holistic approach to risk reduction

Werneth et al. *Health Phys.* 123 (2022) 116.

Should MCM Be Used?

- Sensitivity analysis showed MCM were not effective in reducing risks to meet previous PEL of 3% REID at the 95% confidence level
- The current PEL is based on a dose limit of 600 mSv, which corresponds to 3% mean REID
- Given the current change of PEL, it may be possible for MCM to play a role in a holistic approach for risk reduction to help meet PELs
- Future sensitivity analyses of various plausible Mars mission scenarios may help establish if the benefits of MCM risk reduction outweigh health detriments

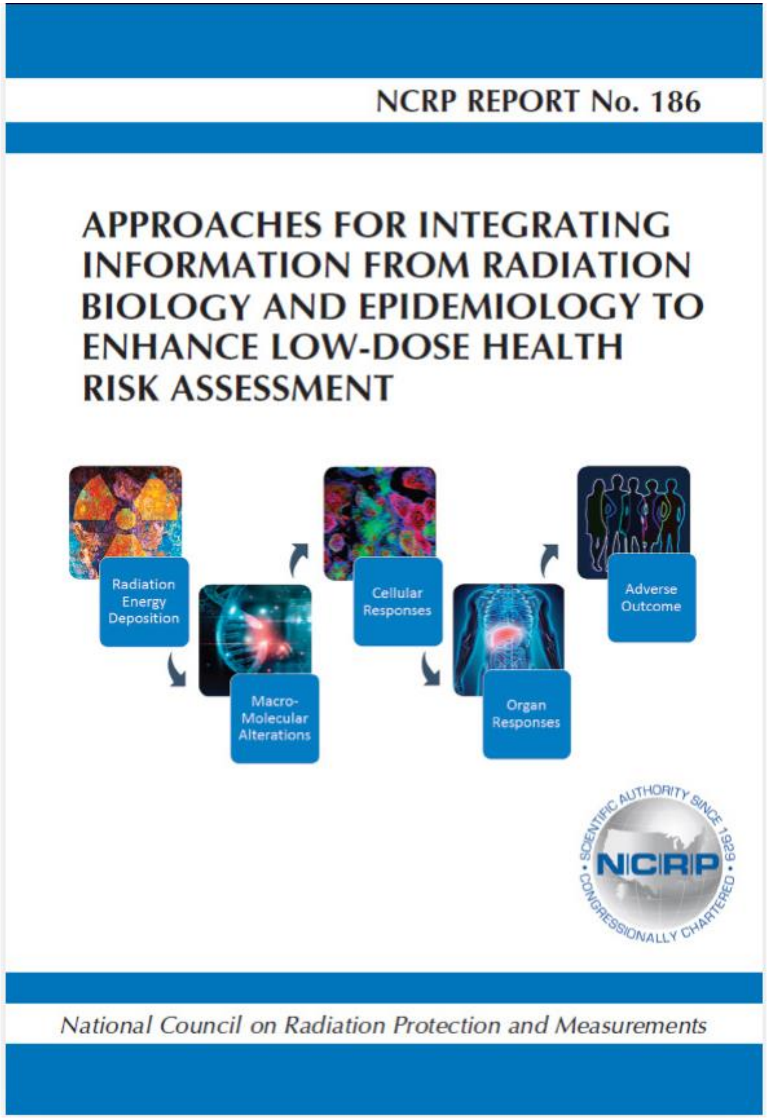
Investigating Mechanistic Models of Risk

Descriptive models

- "…Seek to describe phenotype (e. g. cancer) data without making specific assumptions about causal relationships between variables"—NCRP 186
- For example: LSS atomic bomb study

Mechanistic models

- "…Mathematical representations of specific hypotheses and assumptions about relationship between variables"—NCRP 186
- For example: How normal cells gives rise to malignant tumors and how ionizing radiation affects these biological processes



Investigating Mechanistic Models of Risk

- Identify mechanistic models that describe evolution of background and radiation induced cancer
  - Shuryak and Brenner, Costes, and others
- Determine which key event model parameters would be modified with MCM
  - MCMs have already been demonstrated to reduce background cancer mortality, which leads to REID reduction
  - MCM reduction of radiation risk remains an open question
- Establish framework to incorporate MCM data into mechanistic models as it becomes available
- Estimate reduction in risks for candidate drugs

Mathematical Model of Radiation Carcinogenesis

One Approach: Mechanistic Model of Shuryak et al.

- Short term: provides detailed initial dose-response
- Long term: tracks pre-malignant cell numbers throughout the lifetime
- Radiation initiates, promotes, or kills pre-malignant cells
- A pre-malignant cell generates a clone, if it survives, quickly reaches a size limitation
- The clone then grows more slowly and can eventually generate a malignant cell
- The carcinogenic potential of pre-malignant cells decreases with age (likely from senescence of stem cell and niche function, with age)

Shuryak et al. *Radiat Environ Biophys* **48** (2009) 263.