### Overview of Space Radiation Health Risks with a Focus on Radiation-Induced Cardiovascular Diseases

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#### INTRODUCTION

**Future Manned Missions**

**International Space Station**
- ISS utilizes Space Station Design Reference Mission (SRM) for fixed duration, 2 person crew for 360 days in planning

**Lagrange Points**
- Design Reference Mission currently being formulated
- Columbus EAST magnetosphere and radiation belt
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**Near Earth Objects**
- Design Reference Mission currently being formulated
- Columbus EAST magnetosphere and radiation belt
- Galileo cosmic ray risks are major concern

**Mars**
- 50 followed beyond; exposure Cron, up to 1890 days
- Long-term space missions
- Risks exceed NASA Permissible Exposure Limits (PELs) for cancer, and pose significant non-cancer risks

#### The Space Radiation Problem

- Densely ionizing rays will expose to a high LET, radiation environment compared with low energy cosmic rays and heavy ions (HZE) as well as secondary protons, neutrons, and fragments produced in shielding and tissue
- Heavy ions are qualitatively different from 3- to 10-MeV particles in LET effects, with lower LET and damage to cell nuclei
- Galactic cosmic ray risks are major concern
- Outside Earth's magnetosphere and radiation belts
- Cardiovascular and circulatory changes

#### Health Risks from Space Radiation

**Risk of Radiation Carcinogenesis**
- Mutability and irreversibility, major threat for HZE

**Risk of Acute (In)Flight Late Central Nervous System Effects**
- Possible in flight-risk altered cognitive function including short-term memory, reduced motor function, and behavioral changes which may affect performance

**Risk of Cardiovascular Disease and Other Degenerative Tissue Effects**
- Degenerative changes in the heart, vasculature, and lungs
- Diseases related to aging, including degenerative, respiratory disease, premature senescence, endocrine, and immune system dysfunction

**Risk of Acute Radiation Syndromes due to Solar Particle Events**
- Protruberant effects (nausea, vomiting, diarrhea, fatigue, skin injury, and derangement of the blood-forming organs)

#### Cardiac Disease and Other Degenerative Tissue Effects from Radiation

**Risk of Degenerative Tissue Effects:**
- Diseases related to aging, including degenerative, respiratory disease, premature senescence, endocrine, and immune system dysfunction

**Driving Evidence:**
- Astronauts, bomb survivors, long-term survivors of cancer, survivors of atomic bomb survivors, and medical patients
- Data is contributed by lifestyle factors to a large extent than cancer, especially in bone

**Risk Projections:**
- Recent studies suggest there may be late dose effects and distinct pathologies at low high dose suggesting mechanistic differences
- Impacts of heavy ions largely unknown

#### CCRP Recommendations (2012)

**Definition of "Threshold Dose":**
- Previous CCRP 3000 Report defined a "threshold dose" as an exposure below which clinically significant effects do not occur
- CCRP defined a "threshold dose" as ED1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specific, observable effect only of 1% of individuals exposed to radiation
- ED1 is a dose that is more than an order of magnitude below the baseline levels in unexposed, age-matched, sex-matched, and disease-matched non-exposed human population
- Dose to which the population would receive the already high natural incidence rate or mortality by only 1%
- ED1 does not imply that biological effects occur at lower doses; it merely defines the dose above which a specified effect occurs clinically apparent in a small percentage of individuals

> 0.5 Gy may lead to approximately 1% of exposed individuals developing the disease in question >10 years after exposure. This is in addition to the high natural incidence rate (cirrhosis diseases account for 30–50% of all deaths in most developed countries).

### DRIVING EVIDENCE

#### Radiotherapy Data:

**High Doses > 5 Gy**
- High doses (>5 Gy exposures) associated with damage to the structures of the heart, and to the coronary, cardiac, and other large arteries, including affected arterial stiffness, damage, especially of the pericardium and myocardium, cerebral edema, microvascular damage and sclerosis of the radiated vessels
- No human data exist to estimate risk from heavy ions in space
- Animal models and models with simulated exposure, radiobiology must be applied or developed
- Synergistic readiness of risk under other spaceflight factors

**Moderate Doses 0.5 - 5 Gy**
- Moderate doses (0.5 - 5 Gy exposures) associated with attherosclerosis, micro and macrovascular damage
- Possibly a stochastic reaction
- Mechanisms may involve inflammation and oxidative stress, endothelial dysfunction/vasoresistance

**Low Doses < 0.5 Gy**

#### Meta-Analysis of Low Dose Studies:

- Low doses (<0.5 Gy) associated with systemic effects, microvascular damage
- Possibly a stochastic reaction
- Mechanisms may involve non-targeted effects, kidney dysfunction, monocyte activation, and oxidative stress
- Confounding effects are large

> Although mean cumulative radiation doses were ≥0.2 Gy in most of studies, the small numbers of participants exposed at high cumulative doses (≥0.5 Gy) drive the observed trends in most cohorts with these higher dose groups

#### Low Dose Confounders & Uncertainties

- Suggests increased risks for IHD and non-IHD heart diseases
- Data suggest that circulatory disease risk is significantly elevated only for acute or cumulative doses of about 0.5 Gy and above; data is not statistically significant at lower doses

### Dose Rate Effects

- Tuberculosis patients in Canadian Fluorescent Cohort Study
- $E3,707$ patients (91% unexposed, $96\% <0.5$ Gy, mean dose=0.79 Gy)

### Potential Mechanisms of Radiation-Induced CVD

#### Risk Mitigation Strategy

- Evidence
- Risk Mitigation Strata
- Risk Mitigation Characterization
- Risk Mitigation Strategies: Other determinants

#### Degen Risk Summary

- Association between exposure to high doses of low-LET (≤0.5 Gy) radiation during radiation therapy to the chest and increased risk for development of cardiovascular disease at late times post-exposure is clearly established
- Atomic bomb survivor data and analyses of epidemiology data provide evidence for elevation of risk at lower doses than previously identified, with significant risks at doses as low as 0.5 Gy
- Data at low doses is confounded by lifestyle factors, confounding analyses of epidemiology data below 0.5 Gy
- Effects are considered determinants, with an associated threshold dose; however, recent evidence showing risk at lower doses questions this assumption
- Preliminary risk assessment models being formulated based on recent epidemiology data for lower dose low-LET exposures
- Many risk estimates depend on research results describing the quantitative and qualitative differences between GCR and gamma-rays
- Studies of HZE with HZE and appropriate animal models are required
- Lack of evidence on radiation quality, disease spectrum, latency, and dose rate at low levels of exposures
- The additional mortality and morbidity risks for non-cancer diseases of the cardiovascular system are major concerns because they could increase RED values substantially

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