Uncertainty Analysis in Space Radiation Protection

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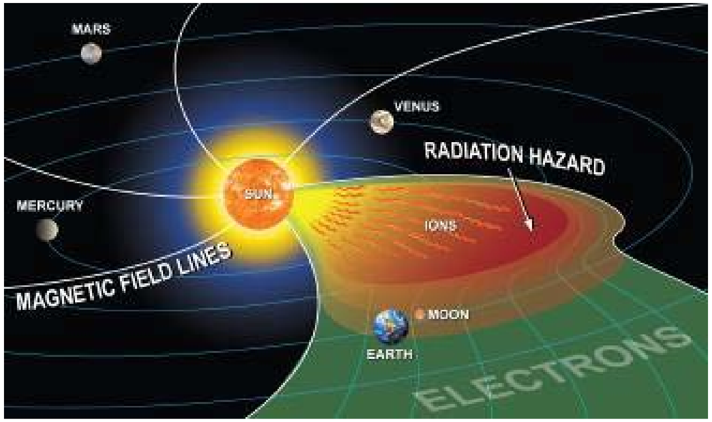
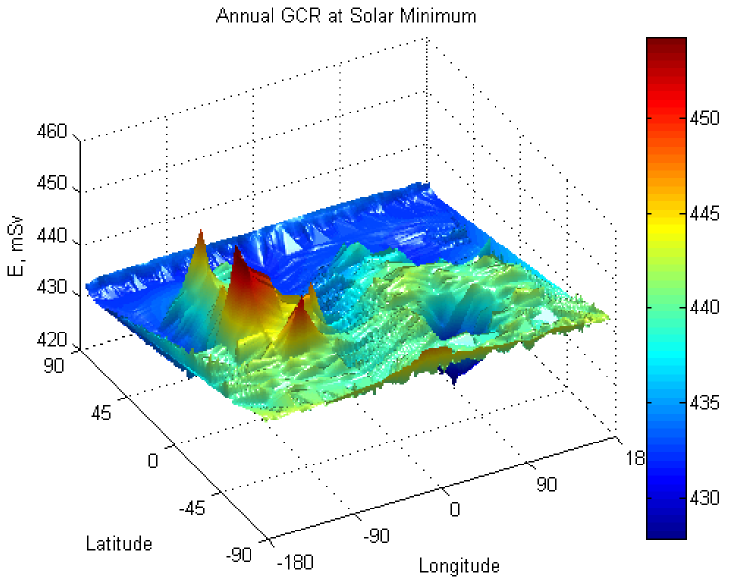
Astronaut Radiation Protection

- NASA is developing new approaches to radiation risk assessment:
  - Probabilistic risk assessment framework
  - Tissue specific risk estimates
- NASA 2010 Model
  - Updates to Low LET Risk coefficients
  - Risks for Never-Smokers
  - Track Structure and Fluence based approach to radiation quality
- Research focus is on uncertainty reduction
  - Smaller tolerances are needed as risk increases, with <50% uncertainty required for Mars
  - NASA Space Radiation Lab (NSRL) experimental program



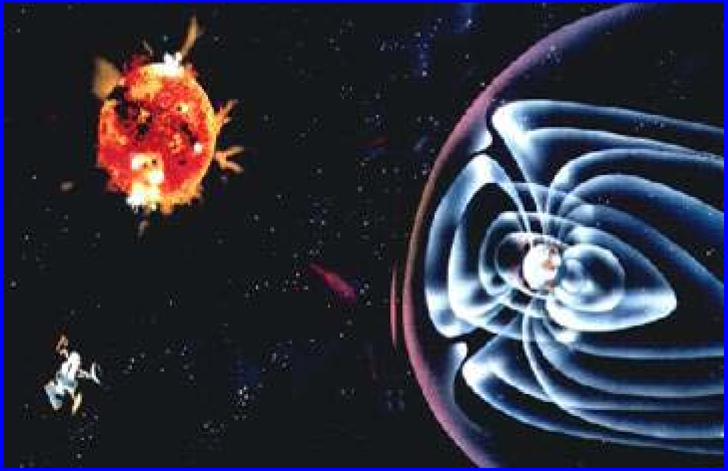


GCR doses on Mars

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



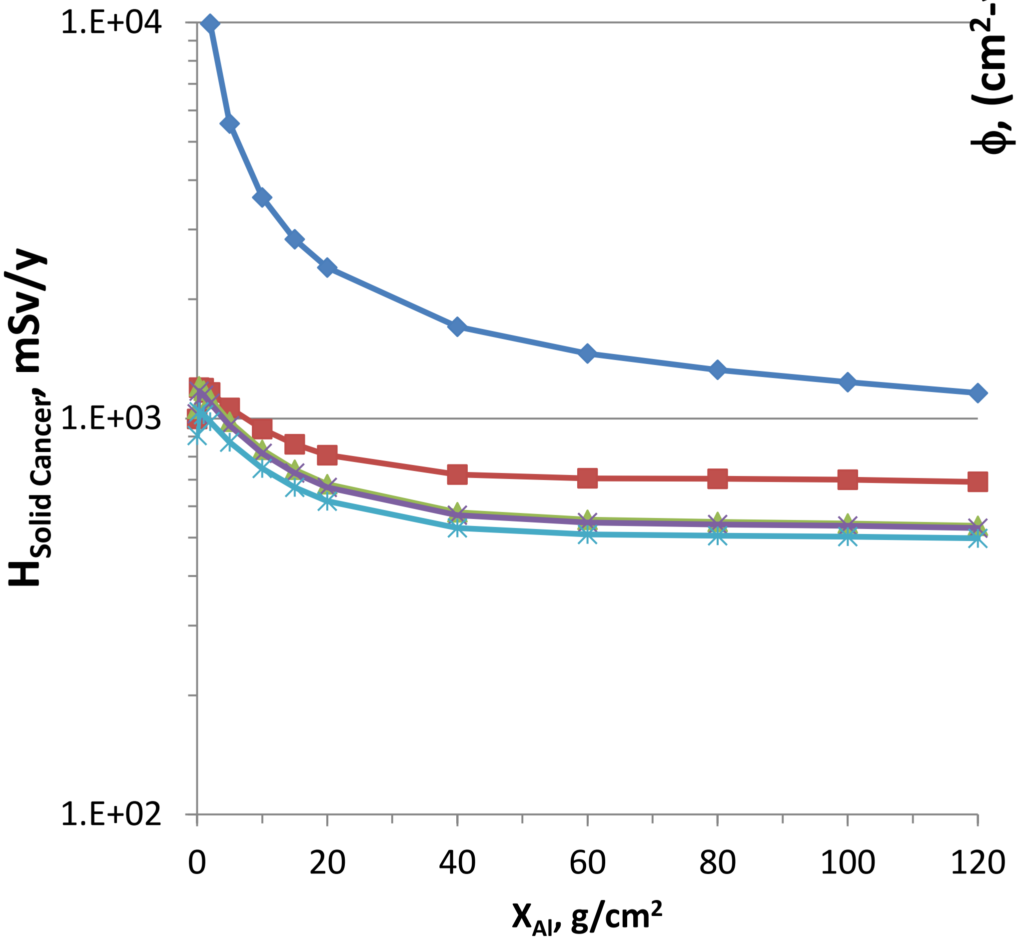
Trapped Radiation:

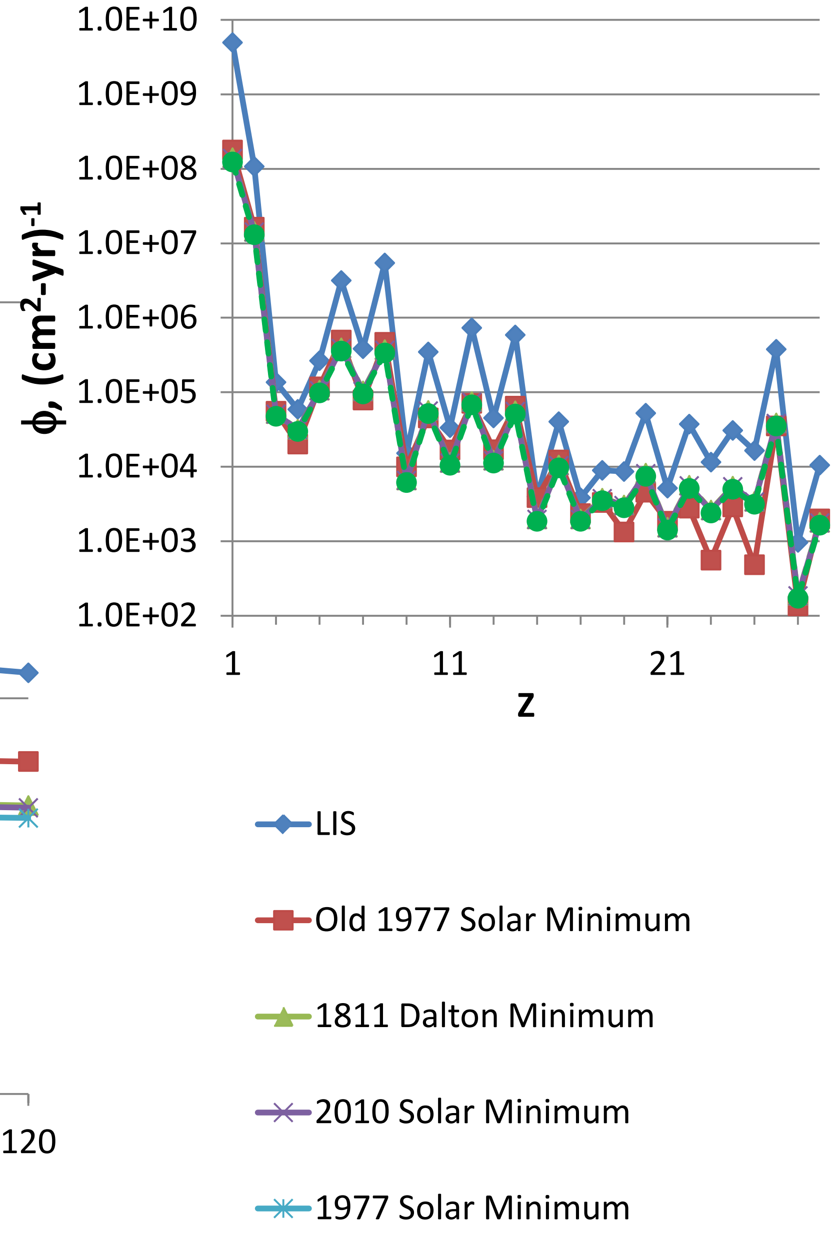
- Medium energy protons and electrons
- Effectively mitigated by shielding
- Mainly relevant to ISS
- MAIN PROBLEM: develop accurate dynamic model

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

Annual Dose Equivalent of Solid Cancer at 1 AU Compared to Deep Space (LIS)





Kim, O'Neill and Cucinotta

Protection Principles & Methods: Earth & Space

- The basic radiation protection principles advocated by the ICPR and NCRP for ground workers are appropriate for space travel:
  - Risk justification
  - Risk limitation
  - ALARA
- However, methods used on Earth are inadequate for space travel:
  - ICRP radiation quality description does not represent HZE radiobiology correctly
  - Specialized group of workers allows more precise risk estimates
  - Missions will approach Risk Limits; thus Uncertainties make it difficult to verify if acceptable risks are exceeded or not
  - Non-cancer risks to the Circulatory and Central Nervous System are an important concern for longer space missions

Recommendations for Space Travel

- NCRP recommends gender and age specific dose limits corresponding to a 3% Excess Cancer Risk (ECR)
  - Strong Age and Gender Dependence of Effective Doses
  - Radiation Quality factor Q(LET) instead of W_R
    - Q(LET) relation from ICRP 60 used to evaluate organ dose equivalent and modified Effective Dose definition
- Past NASA Approach
  - Follow NCRP recommendations on risk coefficients, DDREF, and Q(LET)
  - Risk of Exposure Induced Death (REID) instead of ECR to account for deaths move forward in time by radiation, and for improved comparisons to other space flight risks
  - Because of large uncertainties for HZE particles, 95% Confidence Level as an Ancillary condition to the 3% REID Limit

Recommendations for Revised Projection Model

- Consider recent low LET methods from UNSCEAR, BEIR VII, and Preston et al. (2007)
  - DS02 organ dose estimates and longer follow-up times of A-bomb survivors and related changes
  - BEIR VII recommends incidence based risk transfer, while NCRP Report No. 132 used mortality data transfer
- Risk projection to consider Age, Gender, and Smoking History
  - Never-smokers have reduced radiation risks
- NASA Quality factors derived from Track structure concepts with unique values for Leukemia and Solid Cancer risk estimates
  - Improved Uncertainty analysis for HZE particles
  - Equivalent Fluence based model for risk estimates

Estimating Risks for Astronauts

- Risk estimates are highly dependent on Human data and RBE estimates
- Risk calculations often use Mixture models: weighted averages of the Additive and Multiplicative transfer models
  - Additive model assumes risks are independent of background rates for cancer or other diseases
  - Multiplicative model assumes risks are proportional to background rates for cancer or other diseases
- Astronauts are highly selected- “healthy workers”
  - Excellent nutrition, BMI, exercise, health care, etc.
  - More than 90% are lifetime Never-smokers, however likely exposed to second-hand smoke

Risk Transfer Models

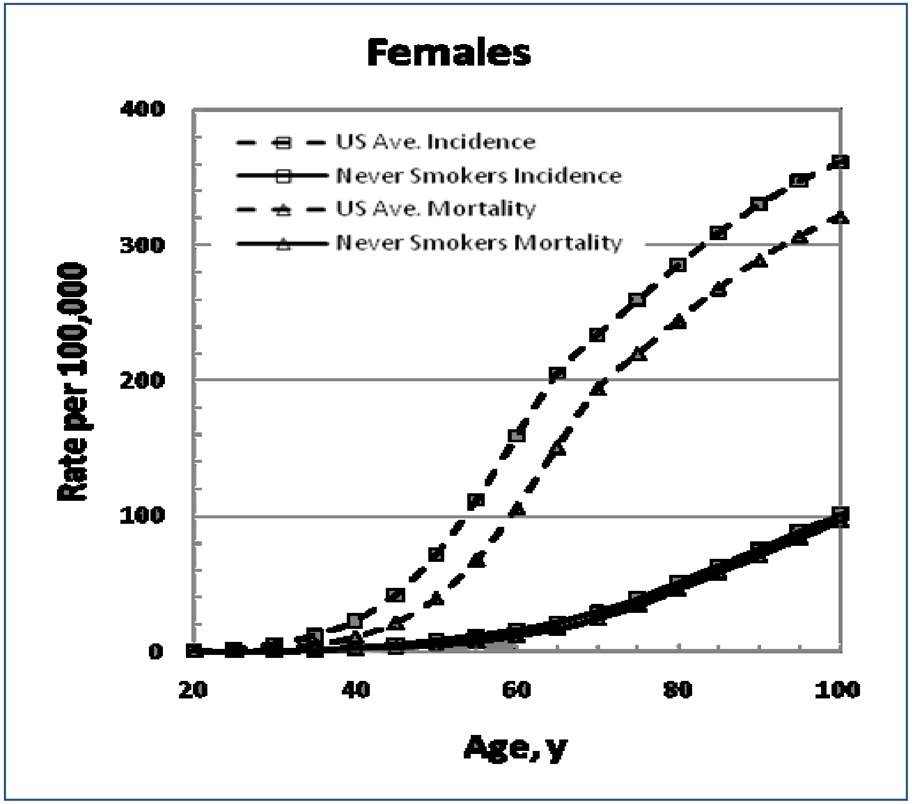
- NCRP 132: <u>Mortality transfer </u>to Ave. U.S. Pop. as mean of Multiplicative and Additive Transfer (weight v_T=0.5) for solid cancer, and Additive transfer for Leukemia
- BEIR VII recommends <u>Incidence transfer </u>with conversion to mortality using ave. U.S. incidence & mortality rates (λ_0):

$$\lambda_M(H_T, a_E, a) \quad = \quad [v_T ERR(a_E, a)\lambda_{0M}(a) + (1 - v_T)\frac{\lambda_{0M}(a)}{\lambda_{0I}(a)} EAR(a_E, a)]\frac{H_T}{DDREF}$$

- UNSCEAR model preferred for EAR and ERR since BEIR ignored age at exposure dependence above 30 y
- Effective Dose does not enter into risk estimate. Instead cancer risk for each tissue is summed using organ dose equivalent
  - Effective dose over-estimates SPE risk by large amount due to age and gender averaging

Radiation Risks for Never-Smokers

- More than 90% of Astronauts are never-smokers
- Smoking effects on Risk projections:
  - Lower risk in Multiplicative Transfer model
  - Epidemiology data confounded by possible radiation-smoking interactions, and errors documenting tobacco use



Thun et al., PLoS Med (2008)

CDC or other Estimates of Smoking Attributable Cancer and Heart Disease for Never-smokers (NS) and US Avg.

Males	RR-Smoker	RR-Former	RR-NS	RR(NS)/US
Esophagus	6.76	4.46	1	0.23
Stomach	1.96	1.47	1	0.67
Kidney	2.72	1.73	1	0.54
Bladder	3.27	2.09	1	0.46
Oral Cav	10.89	3.4	1	0.20
Leukemia	2	1.5	1	0.66
Lung	23.26	8.7	1	0.09
Remainder	4	2.5	1	0.39
Liver	2.25	1.75	1	0.58
Colon	1.19	1.21	1	0.87
Atherosclerosis	2.44	1.33	1	0.63
Cerebrovascular	3.27	1.04	1	0.59

Females	RR-Smoker	RR-Former	RR-NS	RR(NS)/US
Esophagus	7.75	2.79	1	0.31
Stomach	1.36	1.32	1	0.83
Kidney	1.29	1.05	1	0.92
Bladder	2.22	1.89	1	0.62
Oral Cav	5.08	2.29	1	0.41
Leukemia	2	1.5	1	0.70
Lung	12.69	4.53	1	0.20
Remainder	4	2.5	1	0.44
Liver	2.25	1.75	1	0.63
Colon	1.28	1.23	1	0.87
Atherosclerosis	1.83	1	1	0.85
Cerebrovascular	4	1.3	1	0.56

*Radiation risks for Never-smokers are reduced by significant amount compared to US Average due to lower baseline when Multiplicative Risk model is Applied. Remainder estimate based on smoking relate types.

Comparison Group for Astronauts?

- Survival analysis and Standard Mortality Ratio (SMR) suggests Astronauts have much longer life-spans than U.S. avg. or male never-smokers (NS)
  - Median lifespan of Astronauts will likely exceed 90 years

Comparison	SMR	P-value
Astronauts vs. U.S. Avg	0.60	0.0006
Excluding tragedies vs. U.S. Avg	0.35	$<10^{-7}$
Astronauts vs. NS	0.78	0.11
Excluding tragedies vs. NS	0.46	$<10^{-4}$
Astronauts vs. Female NS	1.19	0.24
Excluding tragedies vs. Female NS	0.70	0.073

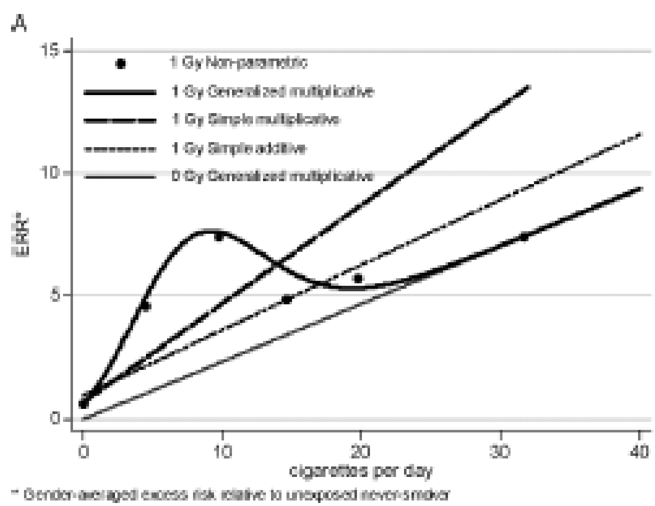
- Longevity of Female Never-smokers similar to Astronaut mortality data

Lung cancer risks in Hodgkin patients exposed to radiation (Gilbert et al.)

Category	Unexposed to radiation cases/controls	Exposed to radiation cases/controls	ERR/Gy (95% CI)	Two-sided P value for testing ERR/Gy=0
Never smokers and unknown	1/33	21/108	0.042 [-0.003, 0.29]	0.092
Current smokers <32 pack-yr	6/13	49/56	0.095 [0.019, 0.33]	0.001
Current smokers 32+ pack years	13/17	52/42	0.35 [0.095, 1.19]	<0.001
Former smokers	6/11	16/52	0.021 [-0.017, 0.27]	0.48

Radiation and Smoking Effects on Lung Cancer Incidence among Atomic Bomb Survivors

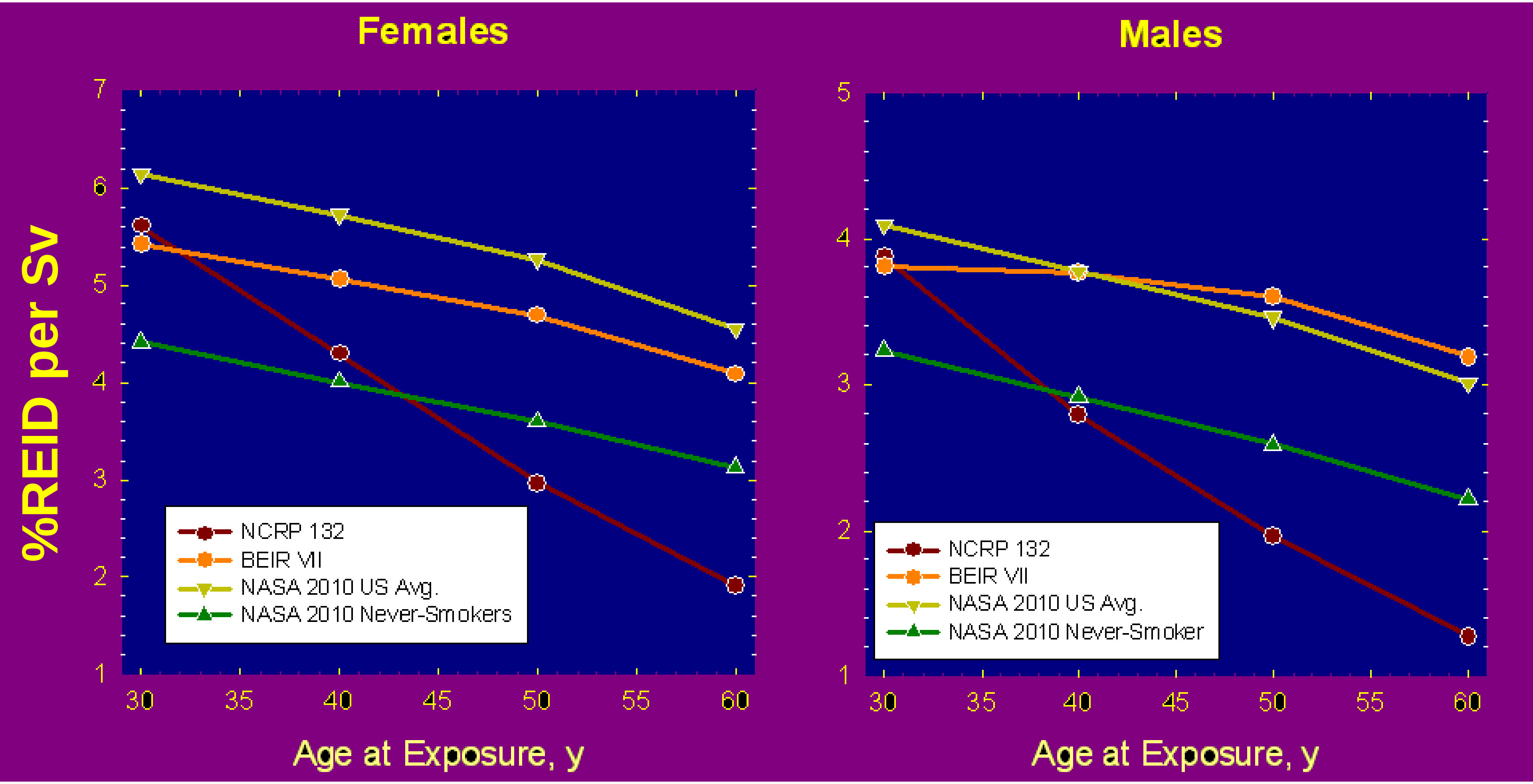
Kyoji Furukawa,[a,1] Dale L. Preston,[b] Stefan Lönn,[c] Sachiyo Funamoto,[a] Shuji Yonehara,[d] Takeshi Matsuo,[e] Hiromi Egawa,[f] Shoji Tokuoka,[a] Kotaro Ozasa,[a] Fumiyoshi Kasagi,[a] Kazunori Kodama[a] and Kiyohiko Mabuchi[g]



Fatal lung cancer risks per Sv (DDREF=2) for NS

		% REID, Females			% REID, Males		
	Age at Exposure	35, y	45, y	55, y	35, y	45, y	55, y
Model Type	**Model rates**	**Average U.S. Population, 2005**					
Additive	BEIR VII	1.20	1.20	1.18	0.65	0.66	0.66
	UNSCEAR	1.28	1.27	1.22	0.71	0.71	0.69
	RERF	1.33	1.34	1.32	0.72	0.73	0.73
Multiplicative	BEIR VII	2.88	2.74	2.38	0.95	0.92	0.83
	UNSCEAR	3.56	3.50	3.23	1.17	1.17	1.11
	RERF	3.71	4.16	4.21	1.13	1.30	1.37
Mixture	BEIR VII	2.04	1.97	1.78	0.80	0.79	0.74
	UNSCEAR	2.43	2.39	2.23	0.94	0.94	0.89
	RERF	2.53	2.77	2.78	0.92	1.02	1.05
		Never-smokers					
Multiplicative	BEIR VII	0.44	0.41	0.37	0.15	0.15	0.14
	UNSCEAR	0.57	0.57	0.54	0.15	0.15	0.14
	RERF	0.55	0.61	0.66	0.14	0.15	0.16
Mixture	BEIR VII	0.85	0.84	0.81	0.40	0.40	0.38
	UNSCEAR	0.96	0.95	0.91	0.46	0.45	0.42
	RERF	0.98	1.01	1.02	0.46	0.47	0.45
Generalized Multiplicative	RERF	0.39	0.47	0.53	0.16	0.17	0.20

Point Estimates of Risk (REID)



BEIR VII choose of v_T=0.3 for Lung (mostly additive “drives” differences

Uncertainty Estimates

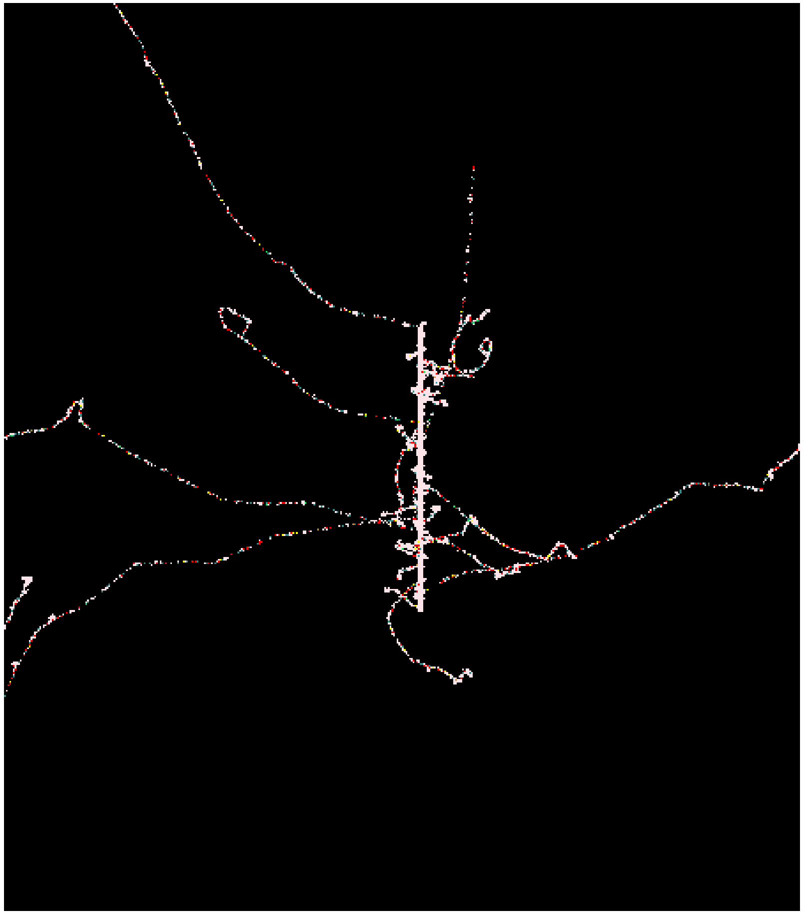
- Subjective Confidence Intervals estimated using Monte-Carlo Propagation over various uncertainties following NCRP 126 approach
- Uncertainties Considered
  - Dose and Dose-rate Effectiveness Factor (DDREF)
  - Radiation Quality Factors
  - Space Physics
  - Statistical and Dosimetry errors in Epidemiology Data
  - Transfer Model Assumptions
- Uncertainties being evaluated
  - Errors in Relative risks estimates for Never-smokers
  - Shape of low dose-rate responses (Non-Targeted or Adaptive Response)
- Uncertainties not considered
  - Error in use of Population based models
  - Interaction with micro-gravity or spaceflight factors

Low LET Uncertainties: Problems for Mars mission

- **Published analysis shows about 2-fold uncertainty for 95% CL before Q and space physics uncertainties are considered**
  - **Statistical, dosimetry, transfer model and DDREF uncertainties**
- **NASA Goal of ±50% error for Mars mission never reached in "Standard Model" due to low LET uncertainties alone**

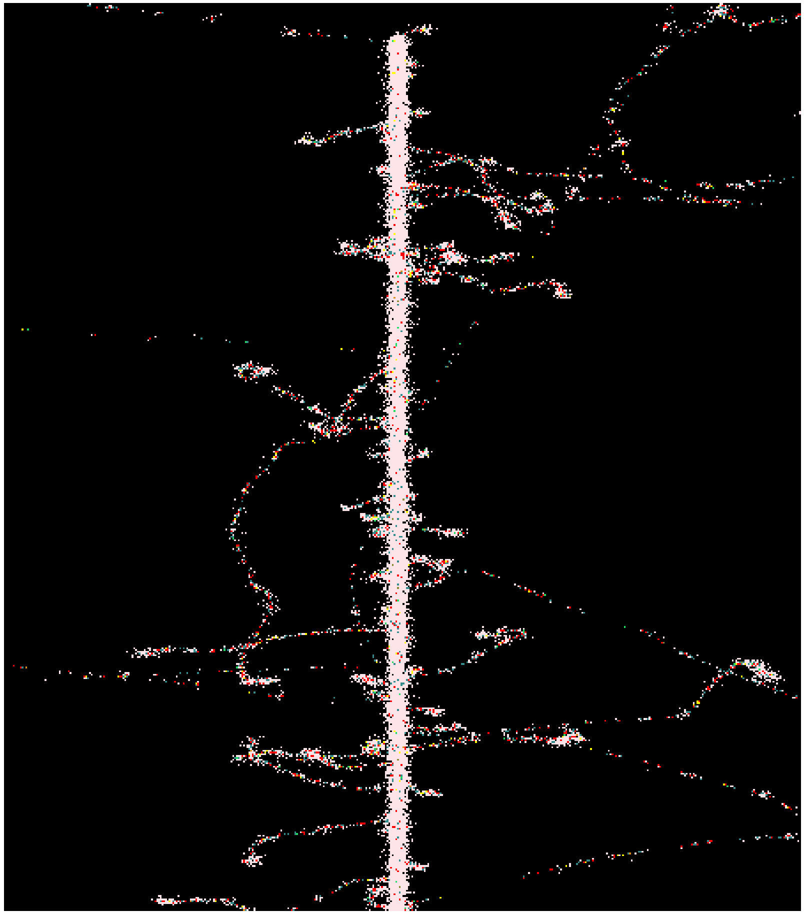
Analysis	%Risk for 0.1 Sv	Comment
NCRP Report 126	0.37 [0.115, 0.808]	Gender avg. with 90% CI
BEIR VII Males	0.48 [0.24, 0.98]	95% CI
BEIR VII Female	0.74 [0.37, 1.5]	95% CI
UNSCEAR Solid Cancer	0.502 [0.28, 0.735]	Gender avg. with 90% CI, DDREF uncert. not considered
UNSCEAR Leukemia	0.061 [0.014, 0.118]	Gender avg. with 90% CI
NASA 2010	0.38 [0.139, 0.76]	40-y Female Never-smoker with 95% CI

HZE Nuclei Tracks (600 MeV/u Iron)



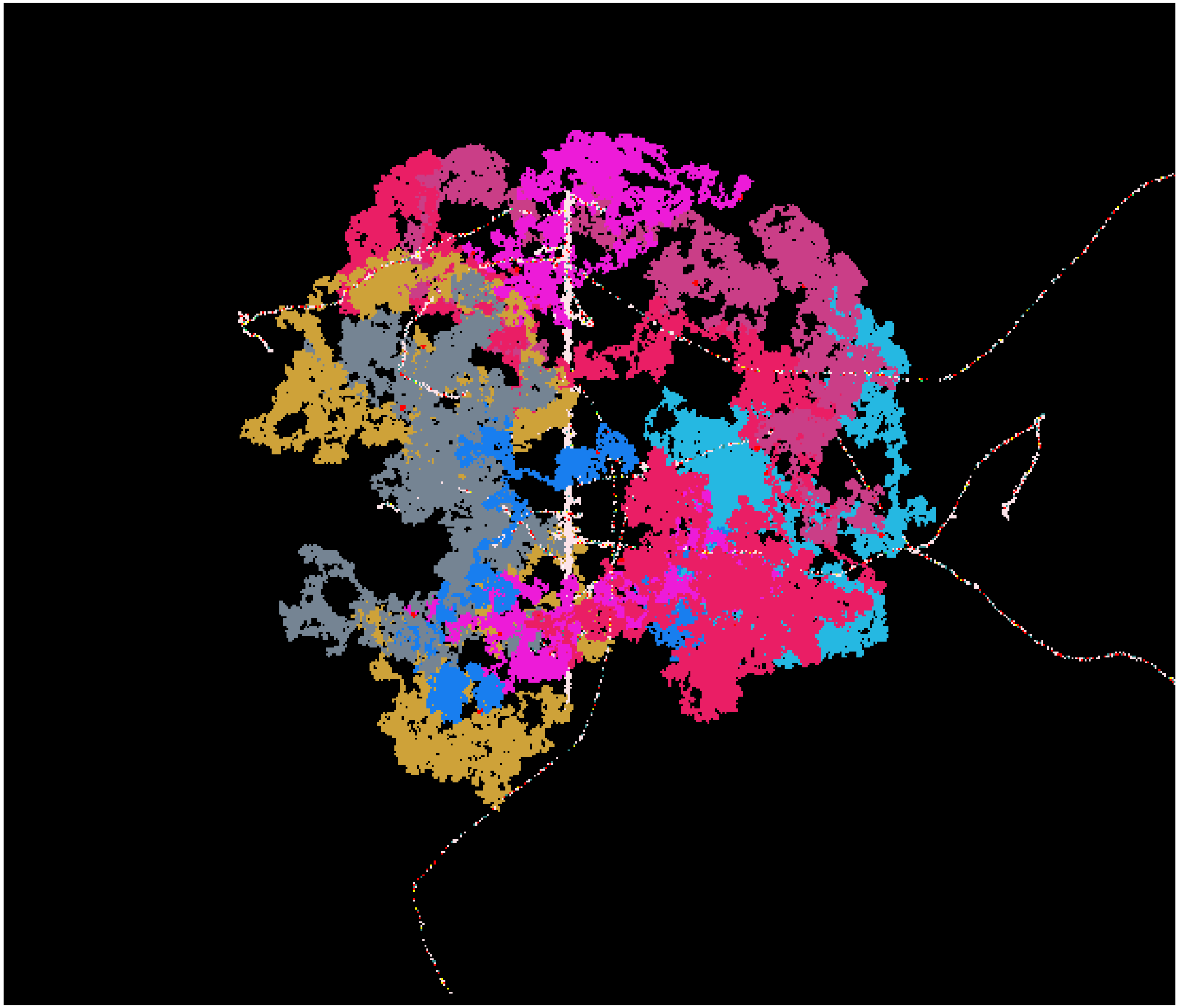
← 10 microns →

Ionization positions from Track showing core and penumbra



Track core region where high ionization density occurs

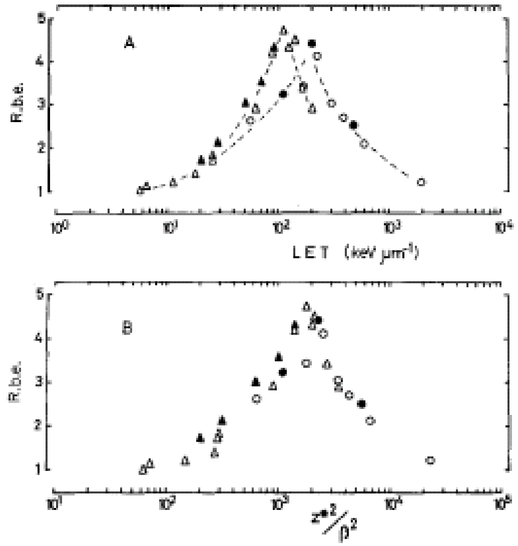
HZE particle Tracks are Distinct from α-particles



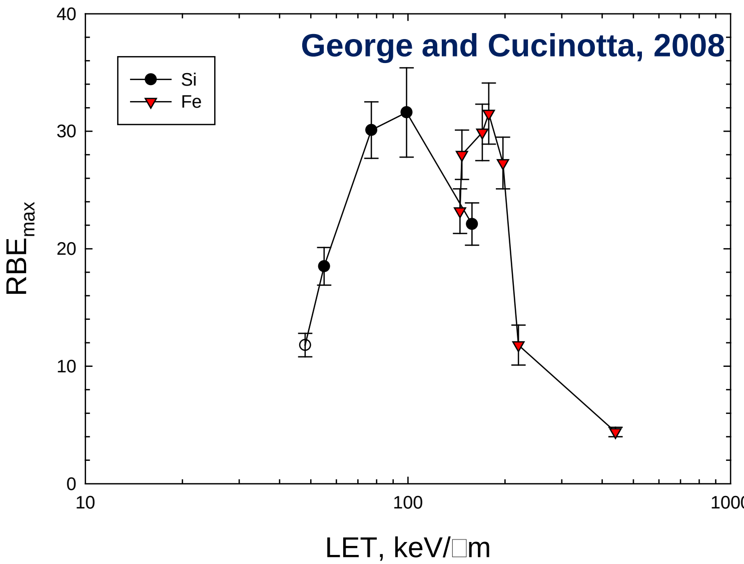
Radiation Quality Descriptions

- Observations from Experiments
  - Energy at peak RBE depends on particle charge number and dose not occur at a fixed LET
    - Increases from less than 100 to more than 150 keV/micron as Z increases
  - RBE depends on charge Z and energy E, and not LET alone
  - At fixed value of LET particles with lower Z are more biologically effective
  - ICRP report (2003) states ion with higher Z has higher effectiveness than lower Z at fixed LET; not supported by track structure models or Expt.'s
  - Slope of rise of RBE with LET is variable with endpoint or biological system
  - Slope of decrease of RBE past peak value is predicted as 1/LET rather than 1/Sqrt(LET) assumed in ICRP 60

Thacker et al. 1979

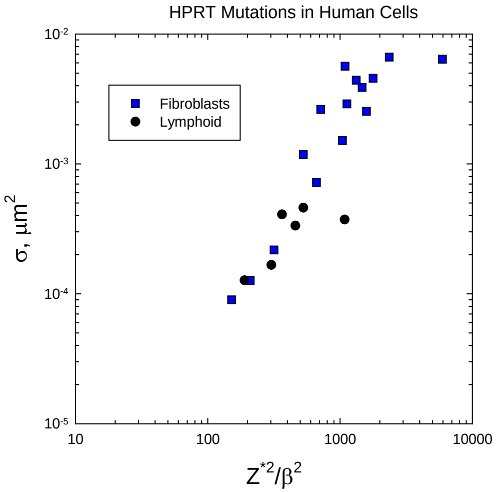


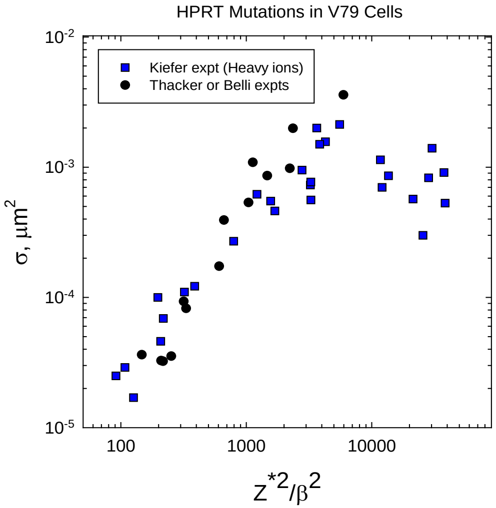
Total Exchanges in Human Lymphocytes

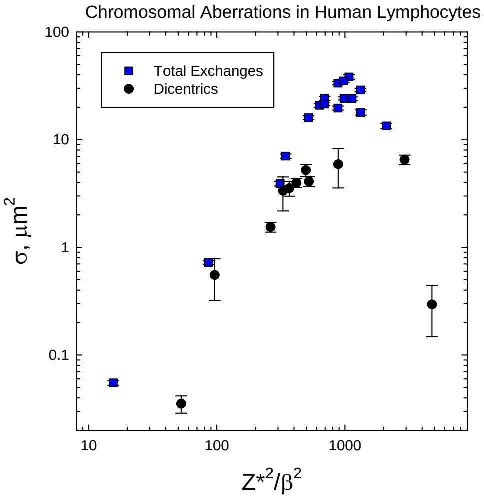


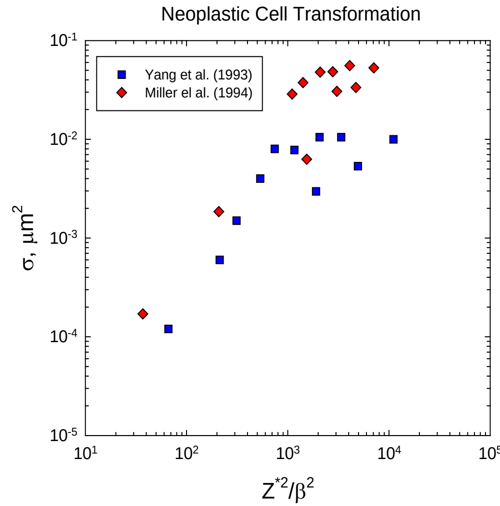
Radiation Quality- Biophysical Considerations

- Action cross section (σ) suggests probability of event per particle saturates at an effective area and declines at low energies
- RBE~σ/LET and therefore declines as 1/LET when saturation value is reached
- For very high Z ions, σ exceeds area of several cell nuclei for cell killing, but not important for GCR
- Z^{*2}/β^2 follows trends in data more accurately than LET, however at low E not a sufficient descriptor
- Endpoints where many ions were studied (mutation, cell kill, aberrations) limited for cancer assessments

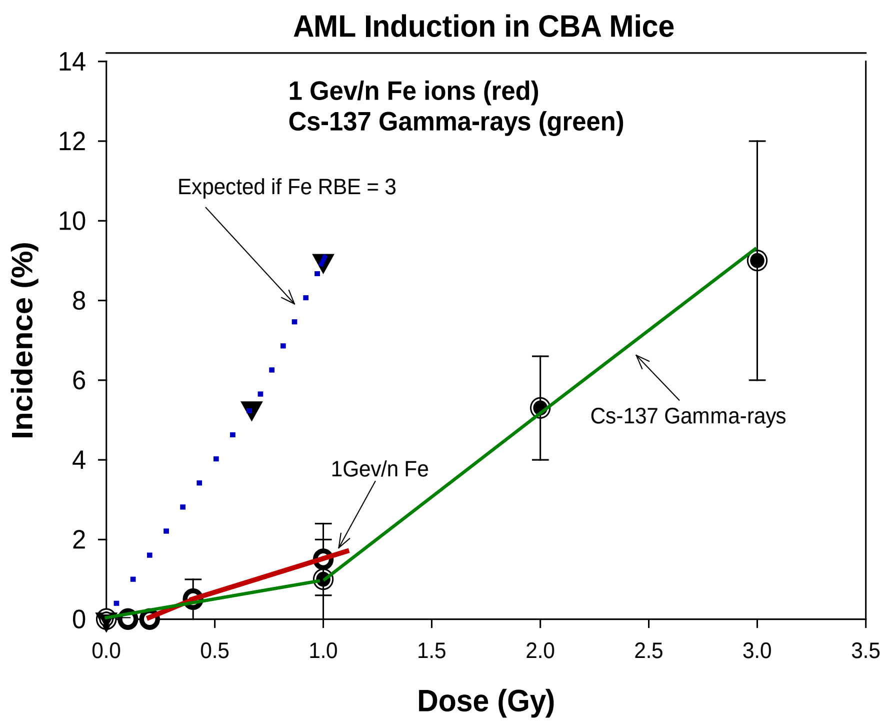


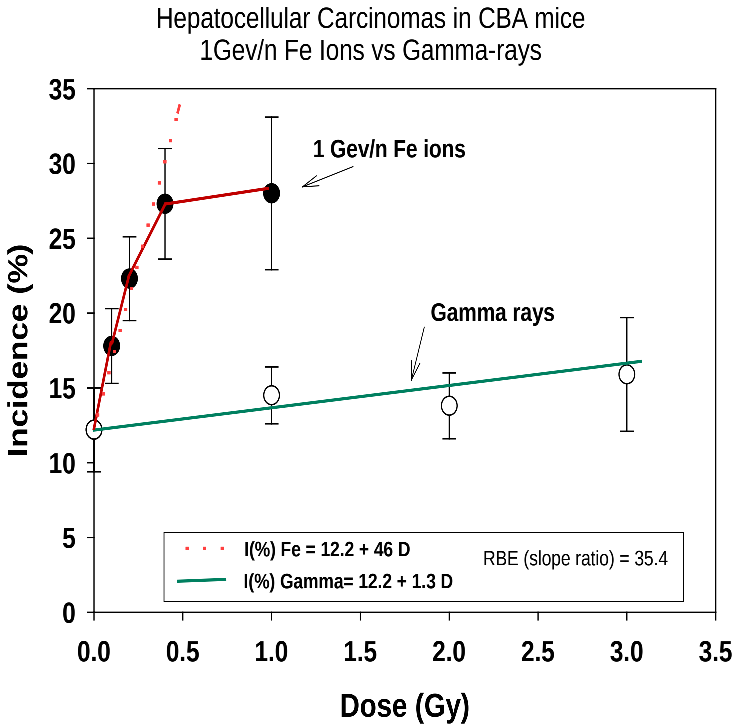






Relative Biological Effectiveness for Fe Particles:
1) Large for Liver and other Solid Tumors (>40)
2) Small for Leukemia (near 1)





Weil, Ullrich et al. Radiat Res. (2009)

NASA Approach to Radiation Quality

- Risk is calculated at tissue sites not using Radiation weighting factors by summing particle fluence (Z, E) weighted by LET and Q(Z,E), or Risk Cross Section, $\Sigma(E,Z)$
- Parameter values informed by existing Radiobiology data:
  - Human data for Thorostrast (Boice et al.), AML data in mice, and human cell culture expt's support Leukemia RBE smaller than Solid Cancer RBE
  - RBE_{max} for Solid Cancers from mice and cellular endpoints suggest very high values occur (range of 10 to 60)
  - RBE_{max} occurs at "saturation point" of cross section for any Z
    - About 70, 100, and 180 keV/μm for Z=1, 14, and 26
  - Decline in RBE past peak and more rapid then 1/Sqrt(LET)
  - Delta-ray effects for relativistic particles should be accounted for in Q model reducing effectiveness for particles > 1 GeV/u
  - Existing data shows E and Z, or Z^{*2}/β^2 better descriptors than LET

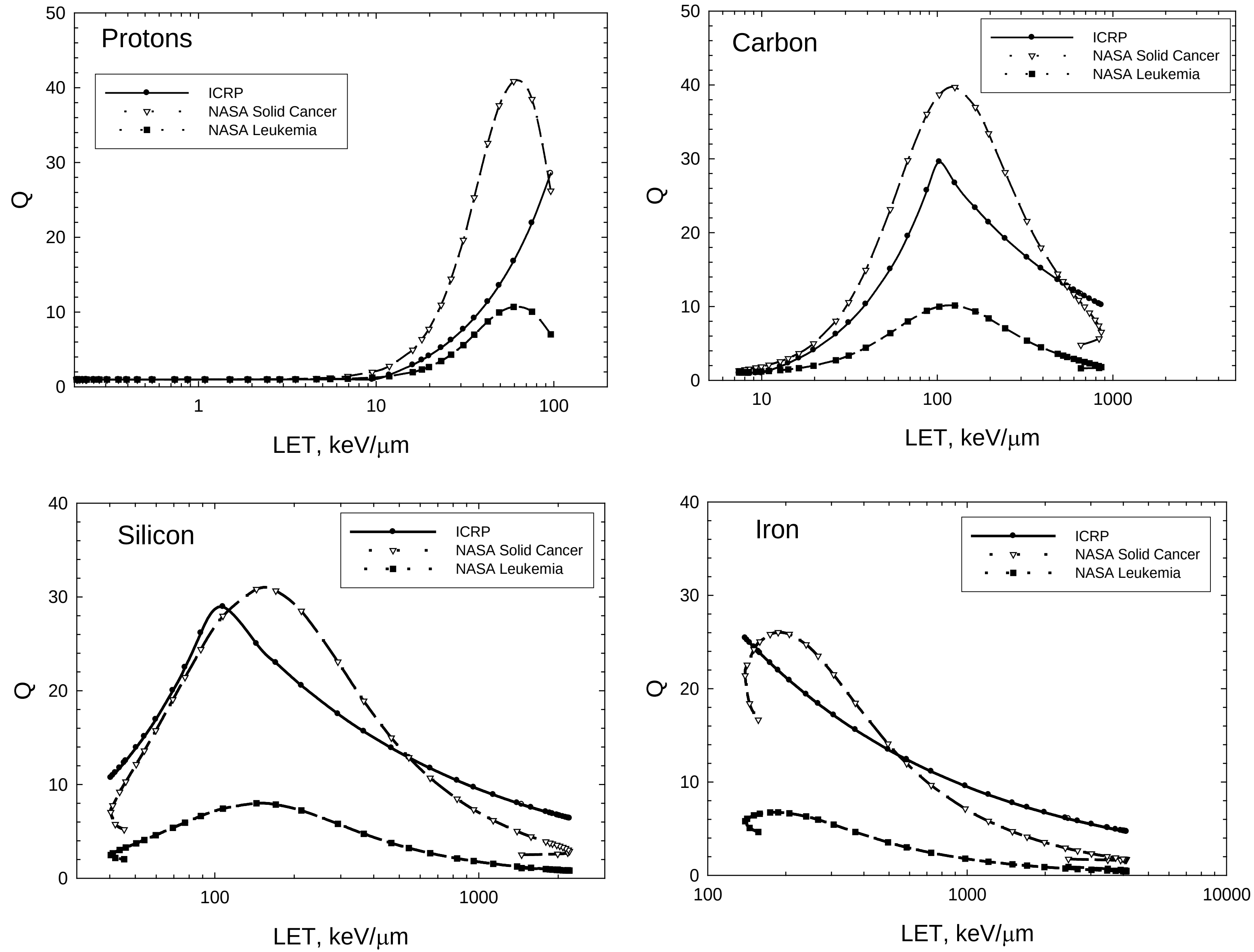
NASA Radiation Quality Model

- Functional forms for Q (or Σ) function will informative and well defined parameters and probability distribution functions (PDF) to support Uncertainty Analysis

$$Q_{NASA} = (1 - P(E,Z)) + \frac{c(\Sigma_0 / \alpha\gamma) P(E,Z)}{LET}; P = (1 - e^{-Z^{*2}/\beta^2/\kappa})^m P_{TD}$$

- Small number of parameters (Σ_0/α_γ, m, and κ)
- PTD low energy correction (<1 MeV/u)
- Peak value for Leukemia set at Q_{max} of 10 and for Solid Cancers at Qmax of 40
- Light ions (Z>5) distinct values from Heavy ions

Comparison to ICRP Model



%REID predictions and 95% CI for NS and Ave. U.S. population for 1-year in deep space at solar minimum with 20 g/cm^2 aluminum shielding

%REID for Males and 95% CI			
a_E, y	**Avg. U.S.**	**Never-Smokers**	**Decrease (%)**
30	2.26 [0.76, 8.11]	1.79 [0.60, 6.42]	21
40	2.10 [0.71, 7.33]	1.63 [0.55, 5.69]	22
50	1.93 [0.65, 6.75]	1.46 [0.49, 5.11]	24

%REID for Females and 95% CI			
a_E, y	**Avg. U.S.**	**Never-Smokers**	**Decrease (%)**
30	3.58 [1.15, 12.9]	2.52 [0.81, 9.06]	30
40	3.23 [1.03, 11.5]	2.18 [0.70, 7.66]	33
50	2.89 [0.88, 10.2]	1.89 [0.60, 6.70]	34

*Reductions more than 50% occur if Multiplicative risk transfer is used for Solid cancers

Maximum "Safe" Days in Deep Space At Solar Min

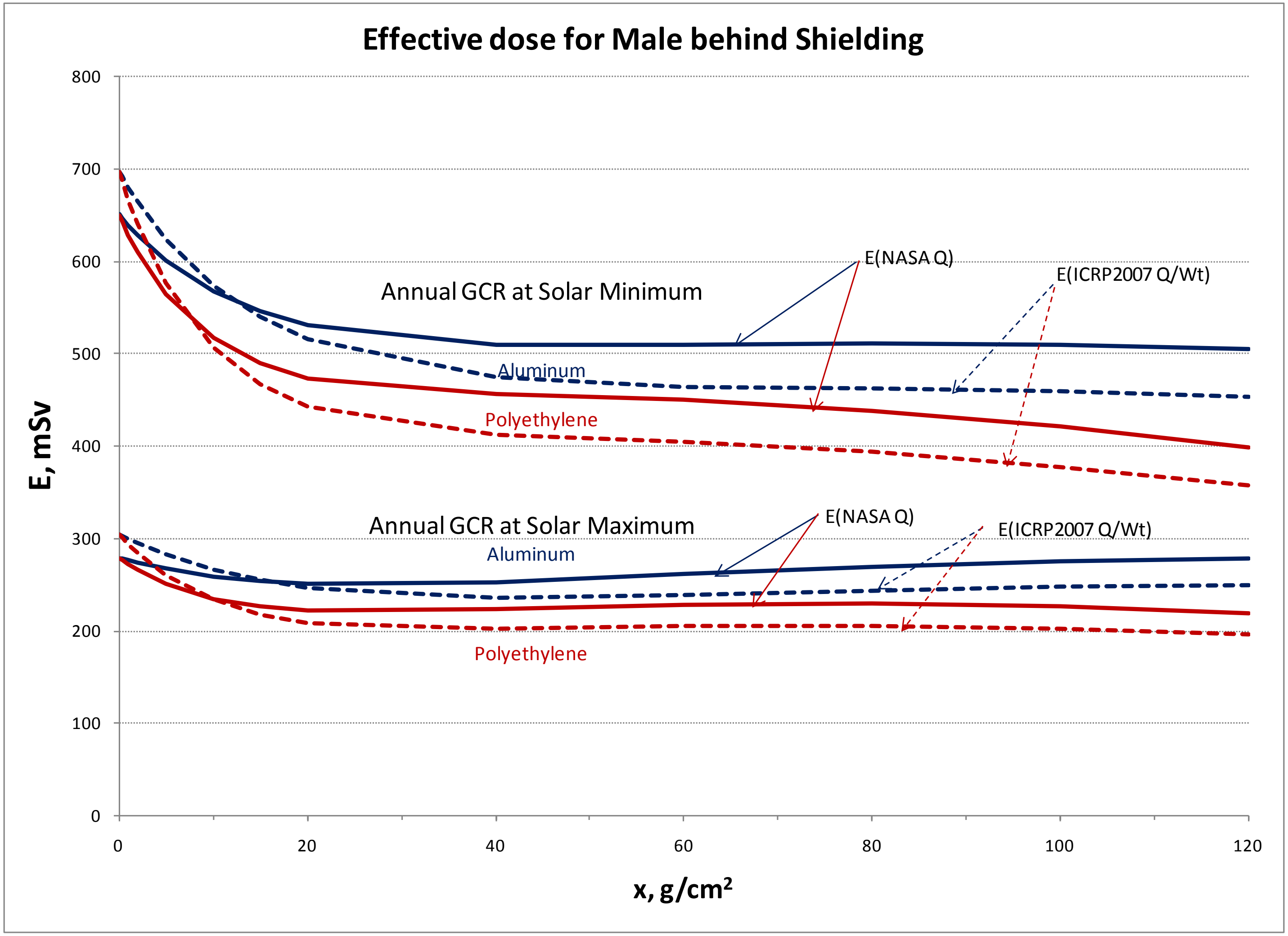
- Uncertainties in Estimating Risks are a Major Limitation to Space Travel
- Maximum Days in Deep Space with heavy shielding to have 95% Confidence to be below NASA Limits (alternative quality factor errors in parenthesis):

a_E, y	NASA 2005	NASA 2010 Avg. U.S.	NASA 2010 Never-Smokers
		Males	
35	158	140 (186)	180 (239)
45	207	150 (200)	198 (263)
55	302	169 (218)	229 (297)
		Females	
35	129	88 (120)	130 (172)
45	173	97 (129)	150 (196)
55	259	113 (149)	177 (231)

Cucinotta, Chappell and Kim, 2011

GCR Shielding Is NOT Effective for All Materials

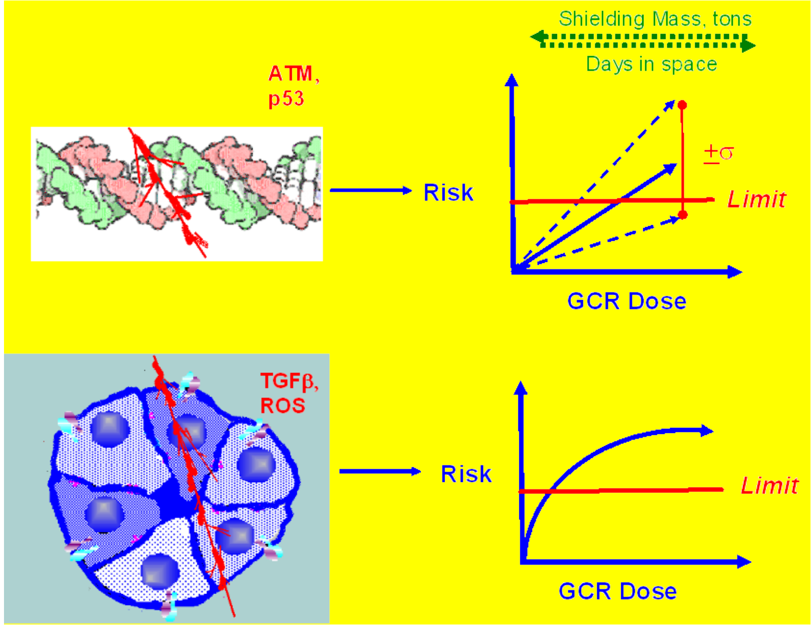
Solar Min and Max Comparison with Proposed NASA Quality Factor (Q) and Tissue Weights (Wt) vs ICRP QF



Non-Targeted Effects and Heavy ions

- Non-targeted effects (NTE) include genomic instability in the progeny of irradiated cells and various bystander effects
- Non-linear or "flat" dose responses observed for many non-targeted effects at low dose
- We find tumor dose responses for Heavy ions is best described by NTE model
- Hypotheses to consider:
  - **Non-linear dose responses for GCR**
  - **Negates importance of mission length and shielding**
  - **Susceptibility to mutations is altered by "change of state" due to aberrant activation of signaling process in chronic exposures to mixed low and high LET radiation**

Conventional vs Non-Targeted Dose Response Models



The Lancet Oncology (2006)

Dose Response Models

- For Heavy Charged Particles most experiments performed at less than one track/cell show that the best representative model is a step-function (Θ) plus a linear dose response:

$$\mathbf{R = R_0 + \kappa\Theta(D_{th}) + \alpha\ Dose}$$

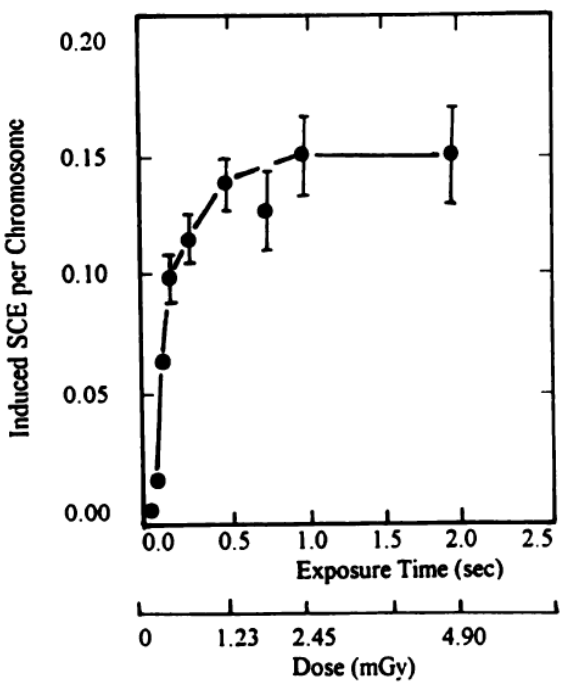
- This model is consistent with NTE model
- Low dose expts. show at moderate or high dose finding a linear dose response should be challenged and not correct
- RBEs in the NTE model will exceed linear extrapolation by a large amount:

$$RBE_{NTE} = RBE_{TE}\ (1 + D_{cross}/Dose);$$

D_{cross} is dose where TE=NTE (~0.05 Gy)

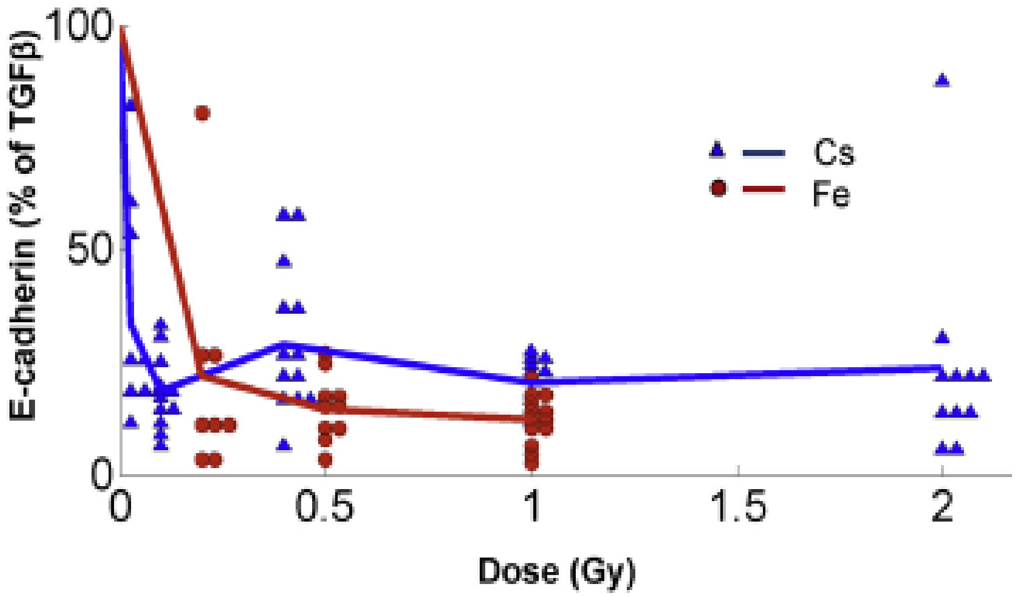
Low Doses of High LET Show Switch Like Responses

SCE from Low Dose Alpha particles

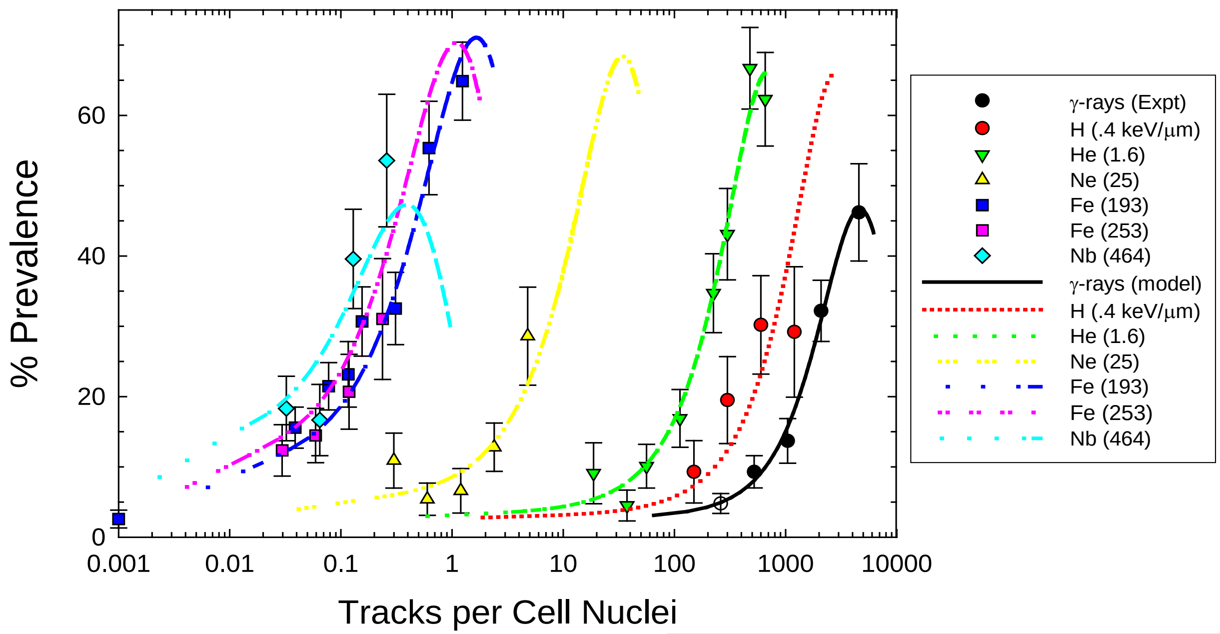


Nagasawi and Little, Can. Res.

Epithelial-mesenchymal transition (EMT) biomarker of HMECs in Matrigel



Andarewewa et al., Int J Rad Onc Biophys



NTE model provides optimal regression fit to H. Gland Tumors in mice

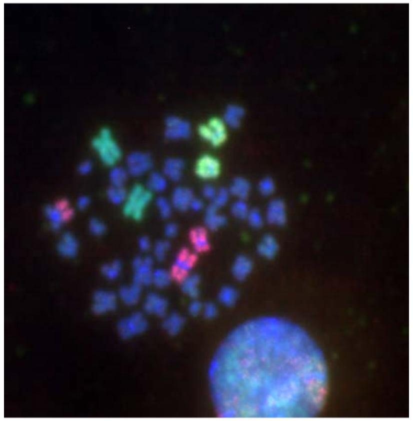
$$P_{NTE} = P_0 + [\alpha(L)D + \beta(L)D^2]e^{-\lambda(L)D} + \kappa(L)e^{-\lambda(L)D}\Theta(D_{th})$$

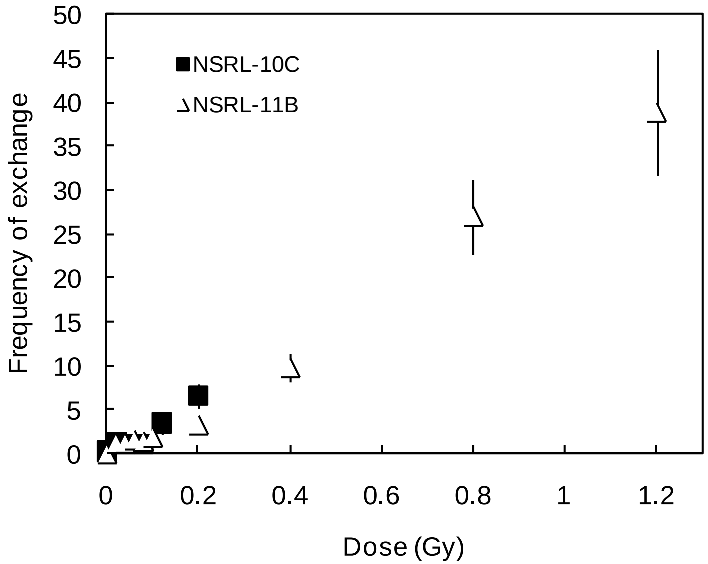
Parameter	*TE Model*	*NTE Model*
P_0	2.93±0.47	2.54±0.4
α_0, Gy^{-1}	7.53±3.96	10.02±2.07
α_1, Gy^{-1} $(keV/\mu m)^{-1}$	1.261±0.213	0.679±0.187
α_2, Gy^{-1} $(keV/\mu m)^{-1}$	0.0037±0.00058	0.0033±.0006
κ_1, $(keV/\mu m)^{-1}$	-	0.12±0.06
κ_2, $(keV/\mu m)^{-1}$	-	0.0053±0.002
Adjusted R^2	0.933	**0.954**
AIC	208.52	**193.6**
BIC	222.42	**209.24**

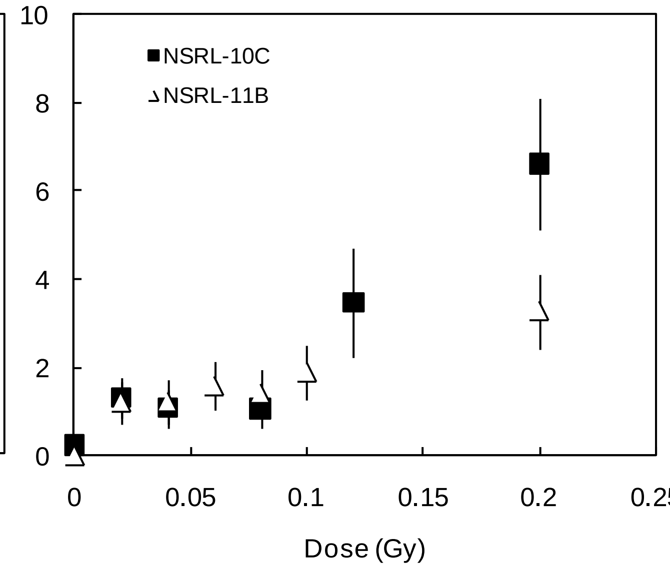
Cucinotta and Chappell, Mutation Res. (2010); Cucinotta *et al.* (2011)

Chromosomal Exchanges in Human Fibroblasts or Lymphocytes

^{28}Si (170 MeV/u; LET=99 keV/μm)







	linear			NTE linear				
	est	se	P-value	est	se	P-value	95% CI	
α	2.56	0.335	0.000	2.204	0.344	0.000	1.53	2.88
κ				0.541	0.187	0.004	0.174	0.908
AIC	4.625			**4.412**				
BIC	-39.7			**-43.3**				

NTE Model provides improved fit over TE model

Summary

Space radiation is a major challenge to Human Exploration:

- Risks are high limiting mission length or crew selection
  - Large mission cost to protect against risks and uncertainties
- More precise methodologies are needed when exposures approach limits
- Major near-term issue is the shape of the low dose response for HZE particles
- Significant risk reduction occurs for Never-smokers
- Research on tissue specific cancer risks is advocated to defined differences in quality, dose-rate, gender, etc.
  - Effective dose is not needed in Space radiation protection

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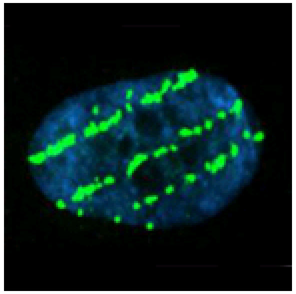

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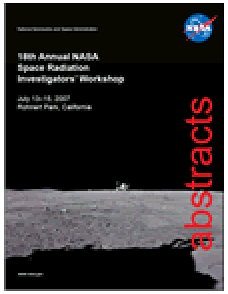
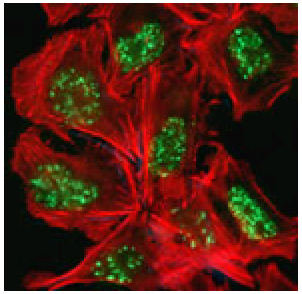
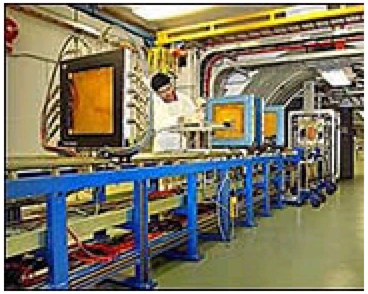


Calendar of Events, Workshops and Conferences



Space Radiation Research



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The Health Risks of Extraterrestrial Environments Encyclopedia

NASA Space Radiation Summer School

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