Cancer and circulatory disease risks for a human mission to Mars: Private mission considerations

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ABSTRACT

In addition to traditional interest by various governments in space exploration, there is growing interest in private missions to Mars and other deep space destinations within the next decade. Private missions could consider persons not restricted by radiation limits; however there remains an interest in the level of risk to be encountered. The major risk for space travel is cancer from galactic cosmic rays (GCR), while circulatory diseases in suggested in some but not all epidemiology studies at modest doses (< 1 Gy) and detriments in cognition are suggested by rodent studies following acute irradiation with moderate doses of heavy ions. The GCR are not easily shielded since they consist of high energy protons, heavy ions and secondary radiation produced in shielding and tissue. Furthermore heavy ions are more effective per unit dose in causing solid cancers compared to gamma-rays. In addition non-targeted effects (NTEs) are suggested by most low dose radiobiology studies to increase biological effectiveness for low doses of high LET radiation. Astronauts and cosmonauts are typically above 40-y, while younger aged persons could participate in private space missions. In this paper, we describe cancer and circulatory disease risks for a 940 d Mars mission for average solar minimum conditions for persons of varying ages from 20 to 60 years. For the first-time NTEs are considered in Mars mission cancer risk predictions. Cancer morbidity risks and 95% confidence intervals for age 20-y persons are predicted as 20.9% [7.04, 51.4] and 12.7% [4.97, 29.3] for females and males, respectively. We find that cancer fatality risks decline with age of exposure while circulatory disease risks are nearly independent of age of exposure. The ratio of cancer to circulatory disease fatalities decreases from about 8-to-1 at 20 y to 5-to-1 at 60 y in females and 4-to-1 and 2.5-to-1 in males with about 2-times higher loss of life expectancy for cancer deaths compared to circulatory related deaths, indicating the much higher importance of cancer risk compared to circulatory disease risks for persons participating in space missions.

1. Introduction

The high costs and need for new technologies involved in long-term human space missions has been a barrier in extending missions outside of low Earth orbit. However, there is growing interest in privately funded missions with several major companies now demonstrating low costs for heavy launch rockets and surface habitats. Private missions could be liberated from occupational radiation limits used for example for the International Space Station (ISS) crews. At this time it is not clear how volunteers or "customers" for a voyage to Mars would consider radiation risks. Possibilities could include signing waivers on radiation risks to companies providing the service, to ignore the risks altogether, or for companies to charge a higher price to customers for additional shielding or potential drugs to reduce their radiation risk.

In addition to the possibility of a mission without risk limitation, the average age of ISS astronauts is typically between 40- to 55-y while younger or older persons may volunteer for private missions. For a Mars mission the galactic cosmic rays (GCR) and possible solar particle events (SPE) present several major health risks such as cancer, cataracts, circulatory diseases, and cognitive detriments. The GCR are difficult to shield against because of their high energies, while the lower energies of SPEs could lead to acute radiation sickness (ARS). However, ARS occurs only above dose thresholds of about 0.5 Gy, with such high doses easily avoided by alert dosimetry and radiation shielding such as a storm shelter. Therefore, cancer risk is also the major risk for SPEs. Radiation cancer risk is known to increase with decreasing age at exposure due to increased tissue sensitivity and longer time after exposure considerations. In contrast to cancer, the risks of degenerative diseases

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such as circulatory diseases, cataracts and cognitive detriments are suggested to increase or remain constant with age of radiation exposure because of the higher levels of background damage at older ages [1,2]. In this paper, we focus on the risks of cancer and circulatory risks from GCR, including risks for lower aged persons (< 40 y) while evaluating the uncertainties in risk estimates.

Risk assessments for long-term space missions are highly uncertain due to lack of knowledge on the radiobiology of high LET radiation such as heavy ions and secondary neutrons [1–7]. In conventional radiation protection on Earth radiation weighting factors or LET dependent quality factors (QF) are used [1,4]. However, in the United States the National Aeronautics and Space Administration (NASA) has implemented space radiation QF's based on track structure concepts [5–7] resulting in QF functions that are dependent on particle kinetic energy per nucleon, *E* and charge number, *Z*. A key aspect of this approach is to estimate uncertainties represented by probability distribution functions (PDFs) for the QF and other factors that enter into cancer risk assessments. More recently, the QF's developed by Cucinotta [3,5] were improved by using data for acute rather than the more uncertain chronic γ–ray exposures as the reference radiation, and eliminating the dependence of the track core on a dose-rate modifier resulting in reduced risk predictions and uncertainties compared to estimates using the previous QFs [8,9].

NTEs include bystander effects where cells traversed by heavy ions transmit oncogenic signals to nearby cells, genomic instability in the progeny of irradiated cells, and tissue microenvironment changes related to cancer development [10–14]. An important issue for risk assessment is a possible deviation from a linear response for high LET radiation at low doses due to NTEs. Mechanistic studies that have used low doses (< 0.1 Gy), where less than one particle traverses a cell nucleus, suggests NTE dominate low dose risk from high LET radiation. We recently made an assessment of the radiation quality dependence of NTE's using radiobiology data with heavy ion beams for Harderian gland tumors in mice and chromosomal aberrations in human cells. A concern is the potential limitation of these experimental models, however we note these are similar to the models used in assigning radiation quality factors in the past [1,4]. The effects of NTEs are shown to significantly increase risk predictions for a Mars mission [15] and a focus of this report. Of concern is that radiobiology studies using heavy ion doses corresponding to more than one particle per cell nucleus (> ~0.1 Gy) will not be sensitive to NTEs, while GCR exposures occur where NTE's are predicted to dominate risks.

In this paper, we discuss predictions of cancer and circulatory disease risks for average populations of different ages (20, 40 and 60-y) that potentially would participate in a Mars mission. The risks of circulatory disease for low chronic doses (< 1 Gy) in human studies shows variability in epidemiological studies, including evidence both for and against a dose threshold [1,7,16]. Also there is significant variations in which type of circulatory risk (e.g. cardiovascular disease (CVD) and ischemic heart disease (IHD), hypertension, etc.) that is associated with radiation exposure in different epidemiology reports [7]. Of note is the circulatory disease risks in the Japanese atomic-bomb survivors show a significant co-morbidity effect between cancer and circulatory disease risk, with much lower circulatory risk indicated when cancer is not present in subjects [17]. We use the results of a meta-analysis of several exposure groups [16] in this report for circulatory risk estimates ignoring a possible dose threshold. Predictions are made for average solar minimum conditions assuming shielding of 20 g/cm^2 of aluminum. The GCR doses decrease slowly with shielding amounts for about 10–100 g/cm^2 with more significant attenuation at higher shielding amounts. Current launch systems would prevent such higher shielding amounts (> 50 g/cm^2) and we expect it to be unlikely to be available for privately funded missions.

2. Materials and methods

2.1. Cancer risk evaluation

We briefly summarize recent methods developed to predict the risk of exposure induced death (REID) for space missions and associated uncertainty distributions [10–13]. The instantaneous cancer incidence or mortality rates, λ_I and λ_M, respectively, are modeled as functions of the tissue averaged absorbed dose D_T, or dose-rate D_{Tr}, gender, age at exposure a_E, and attained age a or latency L, which is the time after exposure $L = a - a_E$. The λ_I (or λ_M) is a sum over rates for each tissue that contributes to cancer risk, λ_{IT} (or λ_{MT}). These dependencies vary for each cancer type that could be increased by radiation exposure. The total risk of exposure induced cancer (REIC) is calculated by folding the instantaneous radiation cancer incidence-rate with the probability of surviving to time t, which is given by the survival function $S_0(t)$ for the background population times the probability for radiation cancer death at previous time, summing over one or more space mission exposures, and then integrating over the remainder of a lifetime [8,9]:

$$REIC(a_E, \ D_T) = \sum_{j=1}^{N_m} \int_{a_{Ej}} dt \lambda_{Ij}(a_{Ej}, \ t, \ D_{Tj}) S_0(t) e^{-\sum_{k=1}^{N_m} \int_{a_E}^{t} dz \lambda_{M_k}(a_{E_k}, \ z, \ D_{Tk})}$$

(1)

where z is the dummy integration variable. In equation (1), N_m is the number of missions (exposures), and for each exposure, j, there is a minimum latency of 5-years for solid cancers, and 2-years for leukemia assumed. Tissue specific REIC estimates are similar to equation (1) using the single term from λ_I of interest. The equation for REID estimates is similar to equation (1) with the incidence rate replaced by the mortality rate (defined below).

The tissue-specific cancer incidence rate for an organ absorbed dose, D_T, is written as a weighted average of the multiplicative and additive transfer models, denoted as a mixture model after adjustment for low dose and dose-rates through introduction of a scaling factor R_{scale} to describe radiation quality dependence and dose-rate reductions:

$$\lambda_{IT}(a_E, a, H_T) = [v_T ERR_T(a_E, a)\lambda_{0IT}(a) + (1 - v_T)EAR_T(a_E, a)]R_{QF}D_T$$

(2)

where v_T is the tissue-specific transfer model weight, λ_{0IT} is the tissue-specific cancer incidence rate in the reference population, and where ERR_T and EAR_T are the tissue specific excess relative risk and excess additive risk per Sievert, respectively. The tissue specific rates for cancer mortality λ_{MT} are modeled following the BEIR VII report [18] whereby the incidence rate of equation (2) is scaled by the age, sex, and tissue specific ratio of rates for mortality to incidence in the population under study:

$$\lambda_{MT}(a_E, a, H_T) = \frac{\lambda_{0MT}(a)}{\lambda_{0IT}(a)}\lambda_{IT}(a_E, a, H_T)$$

(3)

The U.S. cancer rates from 2011 as represented by the DEVCAN software (Version 6.7.2) available from the Center of Disease Control (CDC) are used in this report [19]. DEVCAN provides age, sex and tissue specific incidence and mortality data to ages 95 +.

Risks predictions for circulatory diseases were made in the same manner as our previous reports [5,9]. Circulatory disease risks included cardiovascular disease (CVD) and ischemic heart disease (IHD) using excess relative risk (ERR) estimates from a meta-analysis of studies of atomic bomb survivors, and nuclear workers in several countries [16]. Circulatory disease risk estimates were made using the dose equivalent for the blood forming system (BFO) based on the distinct deterministic effects relative biological effectiveness (RBE) factor compared [1,4] to that of cancer estimates, and without the use of a dose and dose-rate reduction effectiveness factor (DDREF) because the meta-analysis is based largely on chronic exposures. For circulatory disease risks

because the RBE is distinct from the quality factor (QF), organ dose equivalents are expressed in terms of a different unit, Gray-Equivalent (Gy-Eq) [1].

2.2. Space radiation quality factor

The Hazard function is modeled with a dependence on tissue, age of exposure, and time after exposure. Data from low LET radiation epidemiology studies are employed, and the hazard function is scaled to other radiation types and low dose-rates using a scaling factor denoted, R_{QF}. The R_{QF} is estimated from relative biological effectiveness factors (RBE's) determined from low dose and dose-rate particle data relative to acute γ-ray exposures for doses of about 0.5–3 Gy, which we denote as $RBE_{\gamma Acute}$ to distinguish from estimates from RBE_{max} based on less accurate initial slope estimates. The scaling factor is written [20]:

$$R_{QF} = Q_L(Z, E)/DDREF + Q_H(Z, E) \tag{4}$$

where

$$Q_L(Z, E) = [1 - P(Z, E)] \tag{4a}$$

$$Q_H(Z, E) = 6.24\Sigma_0 P(Z, E)/(\alpha_\gamma L) \tag{4b}$$

with the parametric function [20,21].

$$P(Z, E) = [1 - \exp(-Z^{*2}/\kappa\beta^2)]^m [1 - \exp(-E/0.2)] \tag{5}$$

where E is the particles kinetic energy per nucleon, L is the LET, Z is the particles charge number, Z^* the effective charge number, and β the particles speed relative the speed of light. The model parameters (Σ_0/α_γ, κ and m) in Eq. (4) are fit to radiobiology data for tumors in mice or surrogate cancer endpoints as described previously [20,22]. Distinct parameters are used for estimating solid cancer and leukemia risks based on estimates of smaller RBEs for acute myeloid leukemia and thymic lymphoma in mice compared to those found for solid cancers. The LET for protons and helium in tissue are calculated using the National Institute of Standards [23] data. Effective charge is used to scale LET of heavy ions to protons [24].

A key assumption of the model is that the low ionization density part of a particle track is influenced by dose-rate effects as represented by the first term on the right hand side of Eq. (4), while the high ionization density part of a particles track has no dependence on dose-rate as described by the second term on the right-hand side of Eq. (4). A dose-rate modifier is needed for the low ionization density track regions because model parameters are largely derived from radiobiological data at higher doses and dose-rates than those occurring in space, while the usual dose and dose-rate reduction effectiveness factor (DDREF) is used for this estimate.

The space radiation QF model corresponds to a pseudo-action cross section of the form,

$$\Sigma_{TE}(Z, E) = \Sigma_0 P(Z, E) + \alpha_\gamma L[1 - P(Z, E)]/6.24 \tag{6}$$

The Σ is denoted as a pseudo-biological action cross section for tumor induction in units of μm^2 with the designation as "pseudo" given because time-dependent factors have been suppressed, which impact values for the cross-sectional area predicted by fits to the experiments.

2.3. Non-targeted effects quality factor model

In the NTE model we assume the targeted effects (TE) contribution is valid with a linear response to the lowest dose or fluence considered, while an additional NTE contribution occurs such that a pseudo-action cross section is given by,

$$\Sigma_{NTE}(Z, E) = \Sigma_{TE}(Z, E) + \eta(Z, E, F)/F \tag{7}$$

where F is the particle fluence (in units of μm^2) and the η function represents the NTE contribution, which is parameterized as a function of $x = Z^{*2}/\beta^2$ or similarly LET as:

Table 1
Space radiation quality factor model parameters in NTE model.

Model Parameter	Low Z (Z ≤ 2)	High Z (Z > 2)
Slope parameter, m	3	3
κ	624 ± 69	1000 ± 150
Σ_0/α_γ, $\mu m^2 Gy^{-1}$	(4728 ± 1378)/6.24	(4728 ± 1378)/6.24
η_0/α_γ, Gy^{-1}	6×10^{-5}	6×10^{-5}
η_1	833 ± 200	1000 ± 150
A_{bys}, μm^2	2000 ± 1000	2000 ± 1000

$$\eta = \eta_0 x e^{-\eta_1 x} \left[1 - e^{-FA_{bys}} \right] \tag{8}$$

In Eq. (8) the area, A_{bys}, determines the number of bystander cells surrounding a cell traversed directly by a particle that receives an oncogenic signal. The RBE is related to the cross section by $RBE = 6.24 \Sigma/(LET \alpha_\gamma)$ where α_γ is the gamma-ray linear slope coefficient. Therefore, only the ratio of parameters η_0/α_γ is needed for risk estimates.

Model parameters are summarized in Table 1. The parameters η_0/α_γ and η_1 are estimated from low dose radiobiology experiments for mouse Harderian gland tumor induction [25–27] and chromosomal aberrations [22]. The second factor on the right hand side of Eq. (8) describes the "turning on" of NTE at very low doses, which is estimated at about 1 mGy from alpha-particle experiments. The Harderian gland [25–27] and chromosomal aberration experiments [28] do not provide data of sufficiently low doses (< 0.01 Gy) to determine at which dose or fluence level this occurs, and if it depends on radiation quality or the temporal patterns of irradiation. Therefore, the parameter A_{bys} is difficult to estimate and is likely correlated with estimates of η_0. We found for a typical mammalian cell nucleus area of 100 μm^2 that values of A_{bys} of 1000–2000 μm^2 correspond to a NTE signal of about 1-cell layer and A_{bys} of 5000 μm^2 a signal that propagates to about 2 cell layers from a directly hit cell.. These areas suggest interaction distances of up to 50 μm from a directly traversed cell, and a reduction in NTE for doses below about 0.001 Gy (0.1 rad). This value is consistent with low dose α-particle experiments [29], while a longer interaction distance has also been suggested [30]. For calculations we use $A_{bys} = 2000 \mu m^2$ and sample from a normal distribution with a 50% standard deviation about the central estimate.

2.4. GCR exposures

GCR exposures include primary and secondary H, He and HZE particles, and secondary neutrons, mesons, electrons, and γ-rays over a wide energy range. We used the HZE particle transport computer code (HZETRN) with quantum fragmentation model nuclear interaction cross sections and Badhwar–O'Neill GCR environmental model to estimate particle energy spectra for particle type j, $\varphi_j(Z,E)$ as described previously [3,31–34]. These methods agree with spaceflight data in low Earth orbit [3], in transit to Mars [35] and on the Mars surface [36] to within 15% for dose and dose equivalent.

For a TE model, a mixed-field pseudo-action cross section is formed by weighting the particle flux spectra, $\varphi_j(E)$ for particle species, j, contributing to GCR exposure evaluated with the HZETRN code with the pseudo-biological action cross section for mono-energetic particles and summing over all particles and kinetic energies:

$$(\Sigma F)_{TE} = \sum_j \int \phi_j(Z, E)\Sigma(Z_j, E)dE \tag{9}$$

For estimates of NTEs to GCR exposures we assume: 1.) The probability that a bystander cell receives an oncogenic signal only occurs if the fluence is sufficiently high such that a nearby cell is traversed. 2.) The time dependence of the bystander signals is a few days or less such that interactions of bystander signals from different HZE particles can be ignored. 3.) The probability that a bystander cell is transformed by a direct hit at a different time is small and can be ignored. Equations for
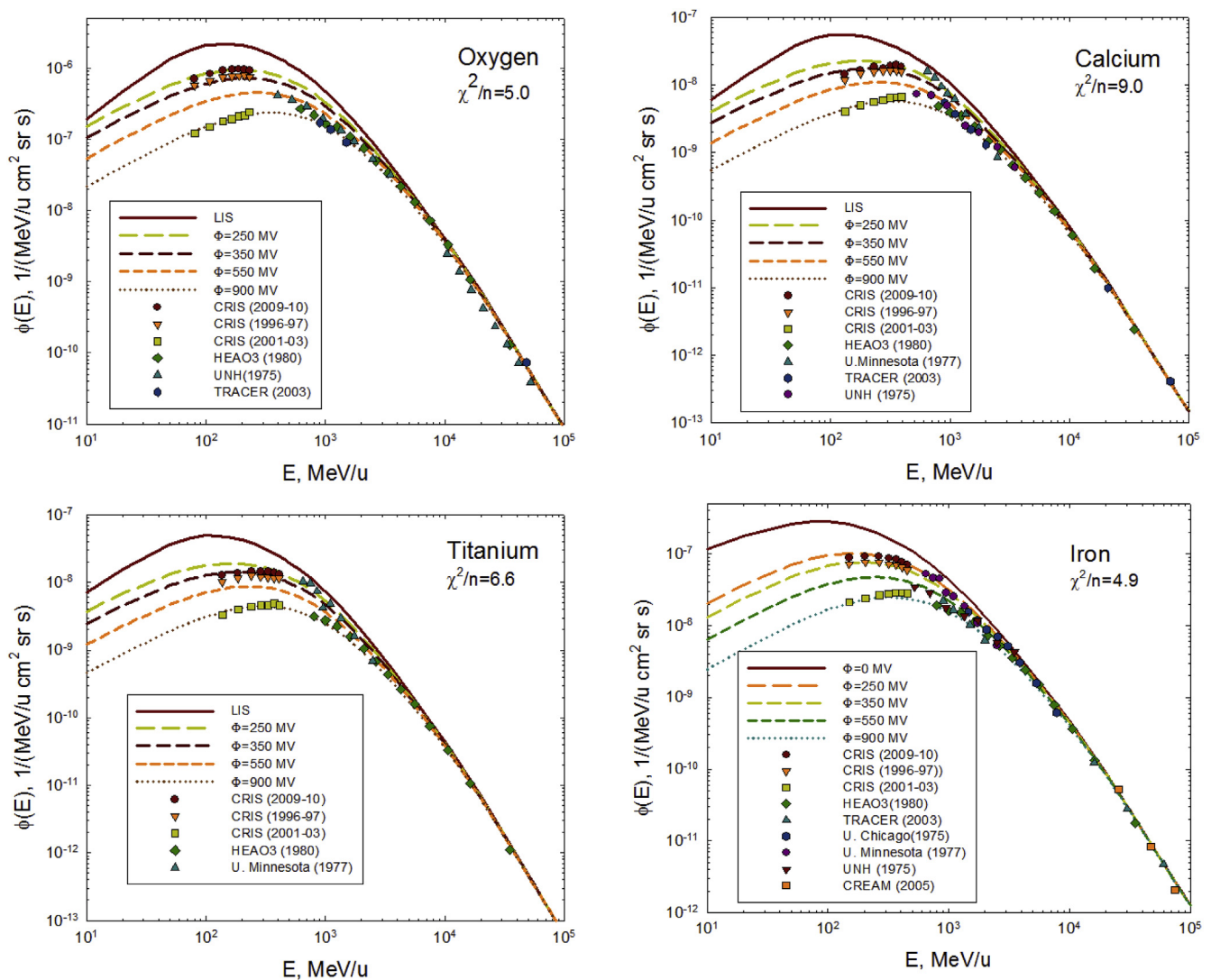
Fig. 1. Comparison of model to measurements for the energy spectrum of GCR O, Ca, Ti, and Fe particles for several times in the solar cycle, and for the local interstellar (LIS) spectra. Model calculations shown are made using the functional form of the energy spectra described by George et al. [37], however with energy dependent slope parameter that varies from about 2.3 at lower energies to 2.7 near 100 GeV/u as fit to data shown.

the mixed-field pseudo-action cross section in the NTE model as folded with particle specific energy spectra as:

$$(\Sigma F)_{NTE} = \sum_j \int \{\phi_j(Z, E)\Sigma(Z_j, E) + \eta_0 x_j \exp(-\eta_1 x_j)[1$$
$$- \exp(-A_{bys}\phi_j(E)]\}dE \qquad (10)$$

Further details on uncertainty analysis of model components are described in previous reports [15,22,27]. We note that uncertainties in particle spectra, dose-rate modifiers, and radiation quality functions are included in our approach.

3. Results

The GCR particles are of high energy with ranges in materials of 10's to 1000's of g/cm². The peak in the heavy ion flux as shown in Fig. 1 is at several hundred MeV/u, however more than 50% of the flux in tissue will be above 1500 MeV/u. Solar modulation reduces the lower energy particle flux near solar maximum [1,37], such that the dose at organs at risk behind average spacecraft shielding varies by about 1.7-fold over the solar cycle and more than 2-fold without tissue shielding. For calculations made here we use an average solar minimum modulation potential of 420 MV a period when solar particle events are not likely to

occur, and average spacecraft shielding of 20 g/cm² of aluminum.

For evaluating risks on the Mars surface a model of the Martian atmosphere is needed. As reported earlier [31,33] we use a CO₂ atmosphere with a mean vertical height of 18 g/cm². We assume 400 d transit to and from Mars and 540 d on the Mars surface. Dose equivalent across the Martian surface can vary by about 50% from 0.2 to 0.3 Sv as reported by Saganti et al. [31] and shown in Fig. 2. Risks could potentially be reduced by about 20% from the mean altitude by choosing a landing site below the mean surface altitude, however this choice might restrict potential science goals. Furthermore for the 940-d mission more than the half of the overall risk is from the transits in deep space to and from Mars, which reduces the potential gains from choosing a Martian habitat at locations below the mean surface. Table 2 compares the model to recent measurements [33,34]. Albedo particles [29], which are of lower energy than primaries, were considered by Kim et al. [29], but are not included in the calculations described here. They are estimated to increase the risks by about 20% on the Mars surface and about 10% overall for the 940-d mission from the results discussed next.

Fig. 3 shows predictions of the relative biological effectiveness factor (RBE) in the NTE model for A_{bys} = 1000, 2000, and 5000 μm² for ⁵⁶Fe and ¹²C particles of typical GCR energies. At a dose of about 0.1 Gy these results limit to the TE (conventional) model of RBE. Fig. 4 shows
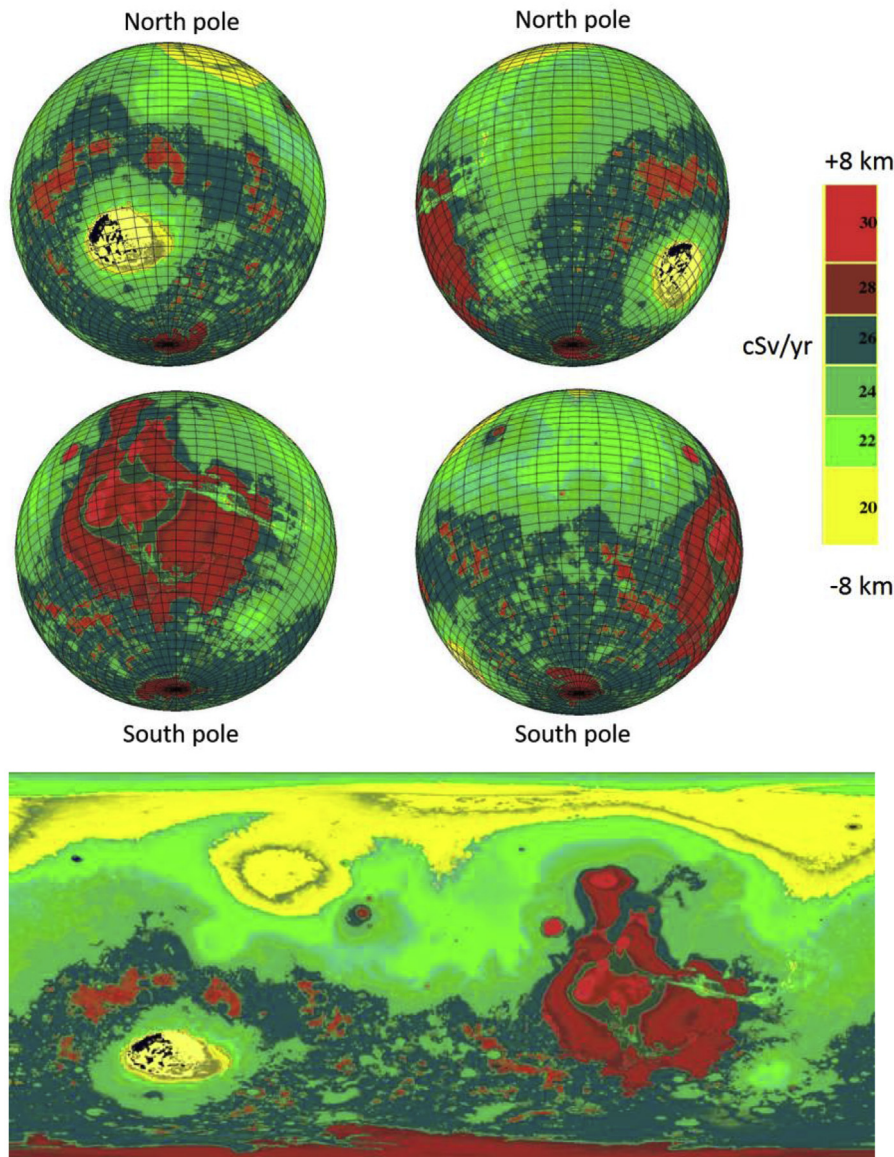
Fig. 2. Results from methods reported earlier by Saganti et al. [31] for the global map of dose equivalent over the Martian surface near solar minimum. The upper panels show Mars at several views using a 90° rotation and the lowest panel shows a 2D representation of the same data.

Table 2
Comparison of NSCR-2012 Model [3,29] to MSL Rad measurements [35,36] for average dose-rate and dose equivalent rate on cruise phase to Mars and on Martian surface.

	GCR DOSE RATE (mGy/d)	GCR DOSE EQUIVALENT RATE (mSv/d)Y
Model Cruise to Mars	0.445	1.80
Model Mars surface	0.21	0.72
RAD Cruise to Mars [35]	0.81 ± 0.08	1.84 ± 0.33
RAD Mars Surface [36]	0.21 ± 0.04	0.64 ± 0.12

the cumulative daily particle fluence spectra above increasing Z^{*2}/β^2 averaged over the 940 day mission. These results include the spacecraft, atmosphere and tissue shielding. The particle spectra have been normalized to hits per area A_{bys} such that distribution plotted represents the average number of particles crossing A_{bys} per day above a given value of Z^{*2}/β^2. These results show that it is very unlikely that more

than one particle with a significant NTE effectiveness ($Z^{*2}/\beta^2 > 10$) as described by Eq. (8) would pass through the small tissue area close to a cell directly hit by a heavy ion within a time-frame of a few days or less. Far fewer particle traversals would occur for particles near the maximum NTE effectiveness ($Z^{*2}/\beta^2 \sim 800$ to 1000). This is in contrast to most radiobiology experiments were doses above 0.1 Gy are used such that most cell nuclei are traversed 1 or more times masking NTEs.

We performed calculations of cancer morbidity and fatality and circulatory disease fatality as caused by GCR for males and females of ages 20, 40, and 60-y as reported in Table 3. Background disease rates for the U.S. average population are assumed. Risks for never-smokers would be estimated at about 20% lower as reported previously [3]. Predictions are for an average solar minimum with the noted 20 g/cm² aluminum shield. The NTE modified radiation quality factors [15,38] are assumed for evaluating solid cancer risks, while NTE are not assumed to contribute to leukemia or circulatory disease risks. These results show in all cases a central estimate above 3% fatality for cancer alone and total fatality risk above 5%. The upper 95% confidence intervals exceeds 10% for all ages and both males and females. Cancer morbidity risks and 95% confidence intervals for age 20-y crew are

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circulatory disease risks. The ratio of cancer to circulatory disease fatalities decreases from about 8-to-1 at 20 y to 5-to-1 at 60 y in females and 4-to-1 and 2.5-to-1 in males with about 2-times higher loss of life expectancy for cancer deaths compared to circulatory related deaths, indicating the much higher importance of cancer risk for persons participating in space missions.

We next considered the average years of loss of life-expectancy (LLE) for different ages of exposure as shown in Table 4. It is important to note that for unexposed persons the average years of remaining life is decreasing with increasing age. The results in Table 4 show that average LLE for cancers is much higher than circulatory diseases, especially at younger ages of exposure with leukemia showing the maximum average LLE of over 30 years for participation in a Mars mission at age 20-y. These results do not take into account the possibility that high LET radiation reduces tumor latency or increases malignancy compared to gamma-rays as suggested by animal studies with neutrons and particle beams [5,9]. The average LLE is reduced at older ages of participation in a Mars mission, however represents a much higher portion of the individuals lifespan compared to the predicted average LLE for younger participants.

4. Discussion

Participants in privately funded missions to Mars are not likely to be restricted by occupational limits used by NASA or other space agencies. However, it is likely that a risk-waiver process would be used and information on potential risks should be clearly stated and well understood in any waiver process. The REID formalism considers the age-dependent competing causes of death for all diseases using an average U.S. population model, and the additional risks and competition from radiation induced cancer and circulatory diseases. We find that the possibility of younger persons participating in a Mars mission would lead to significant increases in cancer risks compared to typical astronaut ages (> 40 y). Older participants would have lower risk but arguably higher detriment because of the higher fraction of remaining lifespan impacted if fatality or morbidity occur. In addition risks of degenerative diseases are likely to be increased for higher ages of exposure. In this report we assumed circulatory disease risks occur without a threshold or dose-rate modifiers which are likely conservative assumptions. Life-style factors such as smoking and obesity can increase diseases background rates which increases risk predictions in the multiplicative risk model, however how such factors influence radiation induced circulatory disease risks is poorly understood.

Evidence for NTE in low-dose responses from exposure to high-LET radiation such as HZE particles has important implications for radiation protection for a Mars mission. Prior reviews [10–14] have described mechanisms for bystander effects in experiments with confluent cultures of fibroblasts or mice, including gap junction communication, release of cytokines and reactive oxygen species (ROS) and TGFbeta signaling. Our previous analysis [15,22,27] shows that low dose data for Harderian gland tumors and chromosomal aberrations are best fit with NTE models compared to the linear response (TE) model used in radiation protection.

The dream of Mars exploration or colonization has led to an active research area and social discussion for several decades. The phasing of such activities with an actual mission has been a confounding factor in making progress in understanding and mitigating space radiation risks. For example if in the 1980's it was known that such missions would not occur until 40–60 years later a more basic investment approach in research would likely have been followed. Limited resources to perform research are often largely dedicated to translational and applied research that becomes obsolete with time as more basic approaches to radiation sciences are discovered and used to address important risk assessment and mitigation questions. For example basic research on NTE's suggest they will likely dominate high LET cancer risks at low doses, however the conventional approach has not included NTEs in
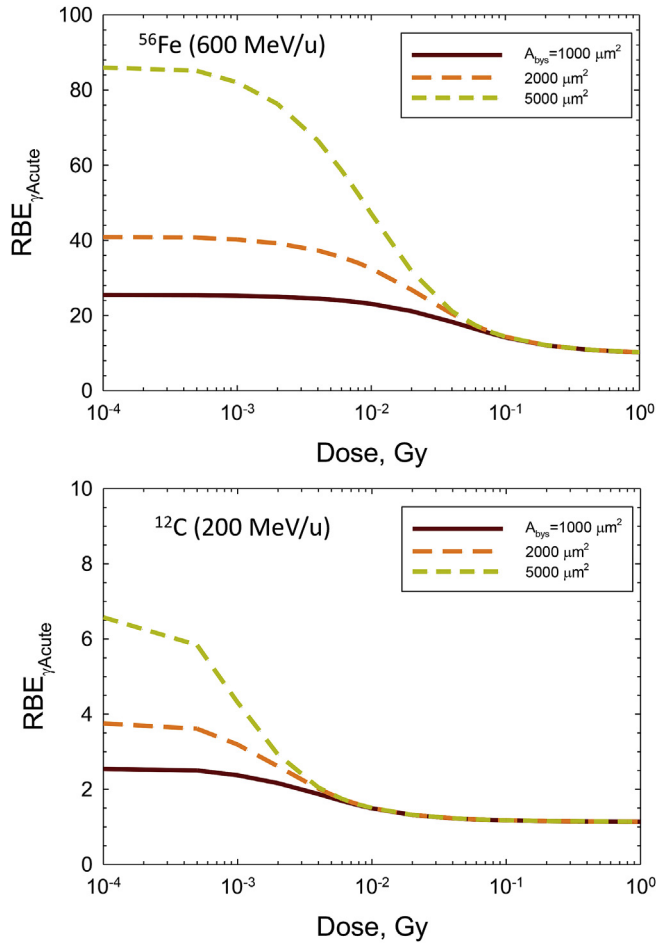

Fig. 3. Dependence of Non-targeted effects RBE model with acute gamma-rays as reference radiation on the effective areas of bystander signal as described in Eq. (8). Upper panel for ^{56}Fe (600 MeV/u) and lower panel ^{12}C (200 MeV/u).
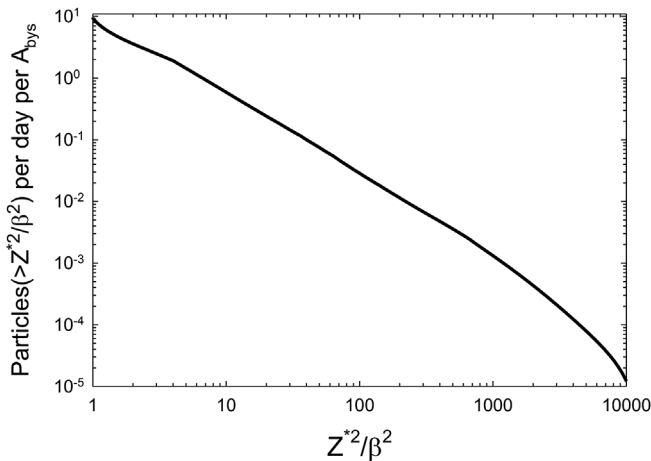

Fig. 4. Results for the cumulative daily particle fluence spectra above increasing Z^{*2}/β^2 averaged over the 940 day mission per A_{bys}. Results include the spacecraft, atmosphere and tissue shielding.

predicted as 20.9% [7.04, 51.4] and 12.7% [4.97, 29.3] for females and males, respectively. The higher cancer risks for a participant of 20-y at age of mission is largely driven by a higher risk overall for all tissues along with especially large increases in thyroid cancer risk for males and females and breast cancer risk for females. We find that cancer fatality risks decline more sharply with age of exposure compared to

Table 3

Predictions of mean and 95% confidence intervals for cancer and circulatory disease risks for average US population.

Age at exposure, y	%REIC (cancer morbidity)	%REID (cancer death)	%REID (circulatory disease death)	%REID (combined probability of death)
Females U.S. Average Population				
20	20.9 [7.04, 51.4]	9.74 [2.71, 21.9]	1.16 [0.48, 2.26]	10.9 [3.45, 22.5]
40	13.2 [3.65, 35.5]	7.59 [2.03, 20.3]	1.2 [0.51, 2.37]	8.8 [2.78, 21.0]
60	8.63 [2.22, 26.0]	5.91 [1.44, 17.8]	1.23 [0.53, 2.49]	7.17 [2.3, 18.7]
Males U.S. Average Population				
20	12.7 [4.97, 29.3]	6.1 [1.96, 14.1]	1.48 [6.3, 2.93]	7.58 [3.38, 15.6]
40	9.28 [3.13, 22.4]	4.94 [1.18, 12.2]	1.54 [0.66, 3.05]	6.49 [2.58, 13.6]
60	6.26 [1.82, 16.0]	3.82 [0.89, 9.69]	1.62 [0.69, 3.19]	5.44 [2.06, 11.3]

Table 4

Predictions of average years of life-loss expectancy if cancer or circulatory disease deaths occur for male and females of several ages of exposures assuming average U.S. population background rates.

Cancer or Circulatory Disease type	Females			Males		
	20-y	40-y	60-y	20-y	40-y	60-y
Leukemia	34.4	23.6	15.0	33.1	22.3	13.9
Stomach	21.2	17.2	11.3	20.4	16.4	10.8
Colon	19.1	17.4	11.9	19.2	17.2	11.6
Liver	16.3	15.1	11.5	16.0	15.0	11.1
Bladder	10.6	10.3	8.9	10.0	9.8	8.5
Lung	14.8	14.3	11.6	13.8	13.3	10.6
Esophagus	19.8	17.1	12.0	17.9	16.0	11.8
Oral Cavity	21.9	19.2	13.1	20.4	17.8	12.1
Brain-CNS	23.6	21.4	14.2	23.8	21.8	13.3
Thyroid	30.6	21.9	13.3	29.1	20.7	12.4
Skin	15.8	13.1	9.4	13.8	11.7	8.8
Breast	16.9	15.2	10.3	–	–	–
CVD	10.3	10.0	9.6	10.3	10.1	9.5
IHD	11.3	11.0	10.2	11.4	11.2	10.2

risk assessments. We have shown NTE's can lead to increases to 2- to 4-fold above the predictions of the conventional model [15,38]. Therefore, more basic studies focused on NTE's are needed along with an important need for mouse experiments at very low doses (< 0.01 Gy) to improve the estimates of predictive model parameters. Because of the important role for persistent ROS damage and signaling, NTEs could require distinct approaches to biological countermeasures and understanding of genetic sensitivity compared to approaches to reduce DNA damage and mutation.

The predictions made in this report of the high level of risks predicted for persons of younger age should be a cause for concern in future discussions of Mars missions. Risks for older participants (> 40-y) are reduced compared to younger ages yet above occupational radiation limits used at NASA. A wider range of radiation associated health risks will arise for private missions without risk limits or the possibility of relaxing the 3% fatality limit used for NASA programs for a Mars mission. Cancer risk occurs at low doses, while degenerative disease risks become important at higher doses or equivalently higher levels of cancer risk acceptance. In this regime, future work should also consider the possibility of cognitive changes [2,39] as well as the possibility of vision impairing cataracts [40–42] during a mission, including the age dependence of such risks. Treatments for rapid onset leukemia's should also be considered because of the shorter latency for leukemia's compared to solid cancers.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.actaastro.2018.08.022.

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