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Predictions of space radiation fatality risk for exploration missions

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ABSTRACT

In this paper we describe revisions to the NASA Space Cancer Risk (NSCR) model focusing on updates to probability distribution functions (PDF) representing the uncertainties in the radiation quality factor (QF) model parameters and the dose and dose-rate reduction effectiveness factor (DDREF). We integrate recent heavy ion data on liver, colorectal, intestinal, lung, and Harderian gland tumors with other data from fission neutron experiments into the model analysis. In an earlier work we introduced distinct QFs for leukemia and solid cancer risk predictions, and here we consider liver cancer risks separately because of the higher RBE's reported in mouse experiments compared to other tumors types, and distinct risk factors for liver cancer for astronauts compared to the U.S. population. The revised model is used to make predictions of fatal cancer and circulatory disease risks for 1-year deep space and International Space Station (ISS) missions, and a 940 day Mars mission. We analyzed the contribution of the various model parameter uncertainties to the overall uncertainty, which shows that the uncertainties in relative biological effectiveness (RBE) factors at high LET due to statistical uncertainties and differences across tissue types and mouse strains are the dominant uncertainty. NASA's exposure limits are approached or exceeded for each mission scenario considered. Two main conclusions are made: 1) Reducing the current estimate of about a 3-fold uncertainty to a 2-fold or lower uncertainty will require much more expansive animal carcinogenesis studies in order to reduce statistical uncertainties and understand tissue, sex and genetic variations. 2) Alternative model assumptions such as non-targeted effects, increased tumor lethality and decreased latency at high LET, and non-cancer mortality risks from circulatory diseases could significantly increase risk estimates to several times higher than the NASA limits.

1. Introduction

Fatality risks for cancer and other diseases due to occupational exposure are a concern for astronauts on long-term space exploration missions where galactic cosmic rays (GCR) and secondary radiation — made up predominantly of high-energy protons, high-energy and charge (HZE) nuclei and neutrons, and possible solar particle events (SPEs) — comprised largely of low- to medium-energy protons will lead to significant organ doses. NASA limits the risk of exposure induced death (REID) due to cancer to no more than a 3% probability at a 95% confidence level (NCRP, 2014). NASA has followed recommendations from the National Council of Radiation Protection and Measurements (NCRP) for setting radiation dose limits (NCRP, 2000; NCRP, 2014). The importance of uncertainties in estimating space radiation risks have been recognized by several reports from the NCRP (NCRP, 1997; NCRP, 2006) and National Research Council (NRC) (NRC, 2013). In 1996 the National Academy of Sciences Space Science Board estimated a 5–10-fold uncertainty for deep space cancer fatality risks (NAS, 1996), while more recent estimates suggest about a 3-fold uncertainty (Cucinotta 2015). There are no epidemiology data for late effects from GCR other than cataracts (Cucinotta et al., 2001; Chylack et al., 2009), while important lifestyle differences in the astronaut compared to other populations occur (Cucinotta et al., 2013a; Cucinotta et al., 2016a). Uncertainties in space radiation risk estimates are dominated by lack of information on the radiobiology of HZE particles that produce both quantitative and qualitative differences in biological effects compared to γ-rays or x rays.

In previous work (Cucinotta et al., 2013a, 2013b) we proposed a new model to estimate space radiation cancer risk that was reviewed by the NRC (NRC, 2013) with further review by the NCRP (2014), resulting in the NASA Space Cancer Risk (NSCR) model-2012 (Cucinotta et al., 2013a). Radiation quality factors (QFs) and

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dose-rate modifying factors, such as the dose and dose-rate reduction effectiveness factor (DDREF), are variables used to scale human epidemiology data for low LET radiation at high dose-rate to the protons, heavy ions and secondary radiation in chronic GCR exposures. Features of the NSCR model include QFs based on track structure concepts with distinct QFs for leukemia and solid cancer risks, a never-smoker model to represent baseline cancer and non-cancer disease risks for astronauts, and use of a cancer incidence to mortality risk transfer methodology. Probability distribution functions (PDFs) for estimating uncertainties in each model parameter were formulated while performing Monte-Carlo sampling over each PDF to estimate an overall REID uncertainty.

Microscopic energy deposition by protons and heavy ions can be described by a track core term representing the direct ionization and excitations of target molecules by primary particles and low energy secondary electrons produced through ionization called δ-rays, and a penumbra term representing the diffuse energy deposition by higher energy δ-rays of low LET, which may extend for 100′s of microns from a particle track for relativistic particles. More recently the QFs used in the NSCR model were revised to further consider track core and penumbra effects in proton and heavy ion exposures (Cucinotta, 2015; Cucinotta et al., 2015). Based on experimental observations for high LET irradiation, no dose-rate modification was applied to the core term, which reduced the overall uncertainties and risk estimates by more than 25% for GCR.

Bayesian analysis has been used to estimate the probability distribution function representing the uncertainty in the DDREF using a prior distribution estimated from the Atomic-bomb survivor data and a likelihood function from certain mouse tumor studies with γ-rays (NAS, 2006). In our previous work we noted that values of RBE's and DDREF's are correlated and therefore estimated model parameters from experiments of mouse solid tumors where both parameters were determined, which formed the basis for our DDREF uncertainty analysis. More recently the BEIR VII reports recommendation of a DDREF of 1.5 has been challenged by Hoel (2015) who shows why the BEIR VII subjective assumptions related to dose truncation of the Japanese atomic-bomb survivors dose response for solid cancer risk are faulty, and suggests that a DDREF of 2 or more is supported by improved analysis. Use of a DDREF of 2 in radiation protection is recommended by the International Commission of Radiological Protection (2007) and the NCRP (2000).

In this paper we present new estimates of probability distribution functions (PDF) representing uncertainties in QF parameters and describe risk predictions for 1-year ISS and space exploration missions. We revise estimates of the QF parameters by analyzing data from cell surrogate endpoints with heavy ions (Cacao et al., 2016), and mouse tumor induction studies with fission neutrons and heavy ions, including recent studies of colorectal and intestinal tumors (Suman et al., 2016) and Harderian gland tumors (Chang et al., 2016). We consider alternatives to the DDREF analysis of the BEIR VII report (NAS, 2006) suggested by Hoel (2015). In addition we augment our previous likelihood function that enters into the Bayesian analysis based on mouse solid tumor data for γ-rays with DDREF estimates from high-energy proton experiments with surrogate cancer endpoints that directly compared high to low dose-rate. The energy distribution of δ-rays from protons is more similar to those of GCR than ^{60}Co γ-rays, however our analysis shows that DDREF from proton experiments are very similar to those found for mouse tumor induction studies with γ-ray irradiations. We also discuss alternative risk assessment assumptions, including higher tumor lethality at high LET, the inclusion of circulatory disease risks, and non-targeted effects. The resulting models are used to make predictions for a 940-day Mars mission and 1-year ISS missions, and the prospects for reducing uncertainties discussed.

2. Methods

2.1. Cancer risk projection model

We briefly summarize recent methods developed to predict the risk of exposure induced death (REID) for space missions and associated uncertainty distributions (Cucinotta et al., 2013a; Cucinotta et al., 2015). The instantaneous cancer incidence or mortality rates, $\lambda_{\rm I}$ and $\lambda_{\rm M}$, 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 until cancer occurrence or death, $L = a - a_{\rm E}$. The $\lambda_{\rm I}$ (or $\lambda_{\rm M}$) is a sum over rates for each tissue that contributes to cancer risk, $\lambda_{\rm IT}$ (or $\lambda_{\rm MT}$). 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, which is taken as 100 years in calculation:

$$REIC(a_{\rm E}, D_{\rm T}) = \sum_{j=1}^{N_m} \int_{a_{{\rm E}j}}^{100} dt \lambda_{Ij}(a_{{\rm E}_j}, t, D_{{\rm T}j}) S_0(t) e^{-\sum_{k=1}^{N_m} \int_{a_E}^{t} dz \lambda_{M_k}(a_{{\rm E}_k}, z, D_{{\rm T}_k})} \quad (1)$$

where z is the dummy integration variable. In Eq. (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 Eq. (1) using the single term from $\lambda_{\rm I}$ of interest. The equation for REID estimates is similar to Eq. (1) with the incidence rate replaced by the mortality rate (defined below).

The tissue and sex-specific cancer incidence rate for an organ absorbed dose, $D_{\rm T}$, is written as a weighted average of the multiplicative and additive transfer models, denoted as a mixture model. However, a scaling factor, R_{QF} is introduced for extrapolating to low dose and dose-rates and estimating the radiation quality dependences of cancer risk for a particle of charge number Z and kinetic energy per nucleon, E:

$$\lambda_{I{\rm T}}(a_{\rm E}, a, D_{\rm T}, Z, E) = [\nu_{\rm T} ERR_{\rm T}(a_{\rm E}, a)\lambda_{0I{\rm T}}(a) + (1-\nu_{\rm T}) EAR_{\rm T}(a_{\rm E}, a)] R_{QF}(Z, E) D_{\rm T} \quad (2)$$

where $\nu_{\rm T}$ is the tissue-specific transfer model weight, $\lambda_{0I{\rm T}}$ is the tissue-specific cancer incidence rate in the reference population, and where $ERR_{\rm T}$ and $EAR_{\rm T}$ are the tissue specific excess relative risk and excess additive risk per Sievert, respectively, with values from the United Nations report (UNSCEAR, 2008). The sex and tissue specific rates for cancer mortality $\lambda_{M{\rm T}}$ are modeled following the BEIR VII report (NAS, 2006) whereby the incidence rate of Eq. (2) is scaled by the age, sex, and tissue specific ratio of rates for mortality to incidence in the population under study in terms of a sex dependent tissue dose equivalent, $H_{\rm T}$:

$$\lambda_{M{\rm T}}(a_{\rm E}, a, H_{\rm T}) = \frac{\lambda_{0M{\rm T}}(a)}{\lambda_{0I{\rm T}}(a)} \lambda_{I{\rm T}}(a_{\rm E}, a, H_{\rm T}) \quad (3)$$

Background cancer, circulatory and pulmonary disease rates that enter the model are updated from our earlier publication (Cucinotta 2015; Cucinotta et al., 2015) using Devcan software (Devcan, 2007) and recent National Cancer Institute (NCI) and Center of Disease Control (CDC) WONDER data bases for the U.S. population (SEER, 2015; CDC, 2015).

R_{QF} is estimated using 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$_{\gamma\rm Acute}$. This approach