Medical Countermeasure Requirements for Meeting Permissible Radiation Exposure Limits in Space

Charles M. Werneth, Tony C. Slaba, and Lisa C. Simonsen
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Acknowledgments

This work was supported by the Human Research Program under the Human Exploration and Operations Mission Directorate of NASA.

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# Nomenclature

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<tr>
<td>EAR</td>
<td>Excess Absolute Risk</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>ERR</td>
<td>Excess Relative Risk</td>
</tr>
<tr>
<td>GCR</td>
<td>Galactic Cosmic Ray</td>
</tr>
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<td>ICRP</td>
<td>International Commission on Radiological Protection</td>
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<tr>
<td>LET</td>
<td>Low Energy Transfer</td>
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<tr>
<td>MCM</td>
<td>Medical Countermeasures</td>
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<tr>
<td>NAS</td>
<td>National Academy of Sciences</td>
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<tr>
<td>NCRP</td>
<td>National Council on Radiation Protection and Measurements</td>
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<tr>
<td>NSCR</td>
<td>NASA Space Cancer Risk Model</td>
</tr>
<tr>
<td>NSRL</td>
<td>NASA Space Radiation Laboratory</td>
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<tr>
<td>PDF</td>
<td>Probability Distribution Function</td>
</tr>
<tr>
<td>PELS</td>
<td>Permissible Exposure Limits</td>
</tr>
<tr>
<td>REID</td>
<td>Risk of Exposure Induced Death</td>
</tr>
<tr>
<td>SPE</td>
<td>Solar Particle Event</td>
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<td>UNSCEAR</td>
<td>United Nations Scientific Committee on the Effects of Atomic Radiation</td>
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Abstract

The space radiation environment consists of ionizing radiation that poses health risks to crew members who embark on a mission to Mars. NASA requires that astronaut career radiation limits for the Risk of Exposure Induced Death (REID) should not exceed 3% at the upper 95% confidence level for cancer mortality. However, the lifetime career limit is likely to be exceeded for even the shortest round-trip mission scenario to Mars. As such, approaches for directly reducing the radiation risk, despite the large uncertainties, are being investigated. A recent study showed that medical countermeasures (MCM) which reduced background cancer mortality rates may be effective in mitigating the REID, where the data employed in the sensitivity analysis were limited to cohort studies of aspirin and warfarin. The present work addresses the general MCM requirements that are needed to meet the lifetime career exposure limits by examining modifications to the background cancer mortality rates, radiation quality factor, and low-LET radiation risk models for a Mars mission scenario. These results may be used to help inform decision-makers about potential experimental measurements that facilitate the greatest propensity for MCM risk reduction.

1 Introduction

This study examines MCM modifications that are necessary to meet NASA Permissible Exposure Limits (PELS) for a Mars mission scenario. A Mars Landing Design Reference Mission (DRM) with a 12 month transit to Mars, 1 month stay on the Martian surface, and 9 month return transit to earth will be used for the calculations herein [11]. The REID will be estimated for a 45 yr old female within aluminum shielding (20 g/cm$^2$) exposed to a Galactic Cosmic Ray (GCR) environment at solar maximum (2001) as modeled by Badhwar O’Neill [16] and the 1972 Solar Particle Event (SPE) as modeled with the King spectrum [9]. Although the King Spectrum is not the most accurate model, it was chosen because it is often used for space radiation studies [20].

The impact of modifying the low-LET excess risk model coefficients, the high-LET component of the NASA quality factor ($Q_{max}$), and the background population cancer mortality rates with MCM will be evaluated in this sensitivity analysis. In order to simplify the sensitivity analysis, it is assumed the three components share no interdependence. The first case considers an MCM that acts by reducing the excess risk from low-LET radiation but has no effect on high-LET exposure risks or background population cancer rates. The second case examines an MCM that acts through a pathway that only mitigates the deleterious biological response of high-LET radiation. The final case considers MCM reduction of background cancer mortality rates, where it is assumed that this has no impact on radiation risk associated with low-LET and high-LET radiation.
This paper is organized as follows. First, the exposure conditions are summarized and
the NASA Permissible Exposure Limits are discussed. This is followed by a review of the
NASA Space Cancer Risk (NSCR) model [3]. Next, a sensitivity study is detailed with
MCM modifications of the following: (1) low-LET risk model coefficients, (2) high-LET
component of the NASA quality factor ($Q_{\text{max}}$), and (3) cancer mortality rates. The core
findings of the study are stated in the Summary. Appendix A reviews the fundamentals
of the low-LET risk models, and Appendix B provides cubic spline interpolations of the
upper 95% confidence limits (CL) for each case that was used to study the efficacy of
MCM in risk reduction.

2 Exposure Conditions

The exposure conditions for a possible Mars mission scenario are summarized below.

- Mars Mission Scenario: Mars Landing DRM
  - 12 month transit to Mars
  - 1 month stay on Martian surface
  - 9 month return transit

- Space Radiation Environment
  - Solar Particle Event (SPE): August 1972 (King)
  - Surface of Mars

- Exposure Age
  - 45 yr old female

3 NASA Permissible Exposure Limits

The NASA permissible exposure limits (PELS) are stated in NASA Standard 3001 [10]:

“Career exposure to radiation is limited to not exceed 3 percent REID
for fatal cancer. NASA assures that this risk limit is not exceeded at a 95
percent confidence level using a statistical assessment of the uncertainties in
the risk projection calculations to limit the cumulative effective dose (in units
of Sievert) received by an astronaut throughout his or her career.”
Figure 1: Median and 95% confidence interval (CI) of a typical REID distribution. The lower 95% confidence level (CL) of 0.2424 corresponds to 2.5% of the area, and the upper 95% CL of 5.5681 corresponds to 97.5% of the area. This figure was reproduced from Werneth et al. [19].

Figure 1 is an example of a typical REID distribution, where the y-axis is the probability distribution function (PDF), and the x-axis is the REID%. The 95% confidence interval (CI) is defined by the lower 95% confidence level (CL) and upper 95% CL. The lower 95% CL corresponds to 2.5% of the area, and the upper 95% CL corresponds to 97.5% of the area.

4 NASA Cancer Risk Model

The current NASA risk assessment model builds on sophisticated radiation risk models of low-LET exposure employed by the National Academy of Sciences (NAS) [12], International Commission on Radiological Protection (ICRP) [6], National Council on Radiation Protection and Measurements (NCRP) [13, 14], Environmental Protection Agency (EPA) [5], and United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [18]. As discussed in section 3, NASA PELS are not to exceed the risk of exposure induced death (REID) for fatal cancer of 3% at the upper 95% confidence level.
For a specific tissue, $T$, the REID is given by [3, 20]

$$\text{REID}_T = \int_{a_E}^{a_{\max}} \lambda^M_T(a, a_E, \nu_T, H_T, \Delta_T) S_0(a|a_E) e^{-\sum_{T'} \int_{a_E}^{a_{T'}} \lambda^M_{T'}(t, a_{E'}, \nu_{T'}, H_{T'}, \Delta_{T'}) dt} \, da, \quad (1)$$

where $\lambda^M_T$ is tissue-specific cancer mortality rate (hazard rate), $a$ is the attained age after radiation exposure, $a_E$ is the age at which radiation exposure occurs, $\nu_T$ is the tissue-specific weighting factor used to assign the proportion of the Excess Relative Risk (ERR) and Excess Additive Risk (EAR) models, $H_T$ is the tissue dose equivalent, $\Delta_T$ is the dose and dose-rate effectiveness factor (DDREF), and $S_0(a, a_E)$ is the conditional probability of surviving to age $a$ given survival to age $a_E$ for the background population for all causes of death [17]:

$$S_0(a|a_E) = S_0(a)/S_0(a_E). \quad (2)$$

The EAR and ERR models are discussed in greater detail in Appendix A.

Hazard rates for the background population are from the National Vital Statistic Reports [15] and are adjusted by the Center of Disease Control risk factors [2] to obtain hazard rates for the never-smoker population. The cancer mortality hazard function is [3, 20]

$$\lambda_T(a, a_E, \nu_T, H_T, \Delta_T) = \nu_T \text{ERR}_T(a, a_E, H_T, \Delta_T) \lambda^M_{0,T}(a)$$

$$+ R^M_T(a)(1 - \nu_T) \text{EAR}_T(a, a_E, H_T, \Delta_T), \quad (3)$$

where $\nu_T$ is the tissue dependent transfer weight between the two models, and $\lambda^M_{0,T}(a)$ is the background cancer mortality rate. $R^M_T(a)$ is the mortality ratio given by [3, 20]

$$R^M_T(a) = \begin{cases} 1 & \text{for BFO} \\ \frac{\lambda^M_{0,T}(a)}{\lambda^M_{0,T}(a)} & \text{otherwise}, \end{cases} \quad (4)$$

where BFO are the blood forming organs where leukemia originates, and $\lambda^I_{0,T}(a)$ is the background cancer incidence rate. With the exception of BFO, the EAR model is based on incidence data for all cancers, and the $R^M_T$ ratio is used to scale the EAR model back to a mortality quantity that is needed for REID. The BFO EAR model is based entirely on mortality data and is therefore not scaled.

The tissue averaged dose equivalent, $H_T$, in units of Sv is evaluated from the differential fluence obtained from radiation transport as [20]

$$H_T = \frac{1}{\rho} \frac{10^8}{6.24} \sum_A \sum_Z \int \phi_T(E, A, Z) LQdE, \quad (5)$$
where $\phi_T(E, A, Z)$ is differential fluence in units of particles/$(\text{cm}^2 \cdot \text{MeV}/\text{n})$ with particles of kinetic energy $E$ in units of MeV/n, charge $Z$, and mass $A$. $L$ is the linear energy transfer in units of keV/µm, and $Q$ is the radiation quality factor that takes into account the biological impact of the incident radiation. $\rho$ is the material bulk density, which for tissue is 1.1 g/cm$^3$.

The NASA radiation quality factor [3] is based on the Katz model [7, 8] and the work of Wilson et al. [21, 22]

$$Q_{\text{NASA}} = [1 - P(Z, E)] + \frac{6.24}{L} \frac{Q_{\text{max}}}{P(Z, E)},$$

where $Q_{\text{max}} = \Sigma_0/\alpha_\gamma$. $P(Z, E)$ is proportional to the Katz action cross section [8], $\bar{P}(Z, E)$, where

$$P(Z, E) = \bar{P}(Z, E) \tau(E),$$

with

$$\bar{P}(Z, E) \equiv (1 - e^{-\chi/\kappa})^m.$$  \hspace{1cm} (8)

$\chi = Z^2/\beta^2$, $Z^* = Z(1 - e^{-125\beta/Z^2/3})$ is the effective charge of the ion [1], $\beta$ is the speed of the particle relative to the speed of light, $m$ is the cell hit number, and $\kappa$ is used to account for the value of $\chi$ for which the action cross section becomes constant [3]. At lower energies, the track structure relative to the biological target size becomes more narrow and is incorporated by modifying the action cross section by a “thin-down” function,

$$\tau(E) = 1 - e^{-E/E_{\text{TD}}}.$$  \hspace{1cm} (9)

Substituting equation (6) into the tissue dose equivalent form equation (5) results in

$$H_T = \frac{1}{\rho} \frac{10^8}{6.24} \sum_A \sum_Z \int \phi_T(E, A, Z) L(Z, E) Q_{\text{NASA}}(Z, E) dE.$$  \hspace{1cm} (10)

$\Sigma_0$, $\alpha_\gamma$, $E_{\text{TD}}$, $\kappa$, and $m$ are all parameters, many of which are estimated from experimental data obtained at the NASA Space Radiation Laboratory (NSRL) [3].

The NSCR model accounts for uncertainty in the radiation quality factor, low-LET risk models, and physics (particle fluence) with uncertainty distributions, which are then sampled with Monte Carlo (MC) techniques [3, 20]. A probability distribution (PDF) for the total REID (summed over all tissues) is obtained from the MC sampling, and the corresponding median and confidence limits are found.
Figure 2: Low-LET risk model modifications. The low-LET risk model coefficients must be reduced by 55% to meet NASA PELS, which is indicated by the red dashed line.

5 MCM Sensitivity Study

5.1 Modification of Low-LET Risk Model

The first sensitivity analysis considers MCM modifications to the ERR and EAR low-LET models. The MCM is assumed to modify the low-LET risk coefficients; however, the high-LET component remains unmodified. This is accomplished by scaling the ERR and EAR models by a factor, $\alpha \in (0, 1]$, where $\alpha = 1$ corresponds to no modification.

$$\lambda_T^{MCM}(a, a_E, \nu_T, H_T, \Delta_T) = \nu_T \alpha \text{ERR}_T(a, a_E, H_T, \Delta_T) \lambda_{0,T}^M(a) + R_T^M(a)(1 - \nu_T) \alpha \text{EAR}_T(a, a_E, H_T, \Delta_T).$$

Equation (11) is substituted into equation (1), and the REID is evaluated for various values of $\alpha$. Note that the hazard function is also included in the exponent of equation (1), so these results are not equivalent to simply scaling the REID by $\alpha$.

Fig. 2 shows the total REID% as a function of percent reduction: $(1 - \alpha)\%$. Median values and 95% confidence intervals (CI) are in blue, and the point estimates are shown in green. The red dashed line indicates the NASA career radiation exposure limit for fatal cancer of 3% REID at the upper 95% CL. The 0% reduction is the total REID% for
the mission with no MCM intervention. As expected, the median, point estimate, and upper 95% CL decrease as a function of percent reduction of the low-LET risk coefficients. Tabulated values are given in Table 1. The cubic spline interpolation of the upper 95% CL in Appendix B shows that a 55% reduction is required to meet NASA PELS for fatal cancer.

5.2 High-LET Component of NASA Quality Factor

The greatest uncertainty in the estimation of the REID is the biological impact of space radiation exposure [4]. The NASA radiation quality factor consists of a high ionization-density component associated with high-LET radiation and a sparsely ionizing component associated with delta ray electrons. MCM modifications to the low-LET component was considered in the previous section through the ERR and EAR low-LET risk models. In the present section, the MCM is assumed to act only on the high-LET component of the NASA quality factor. This is studied by scaling the maximum of the NASA quality factor, $Q_{\text{max}}$, by $\alpha$,

$$Q_{\text{NASA}}^{\text{MCM}} = [1 - P(Z, E)] + \frac{6.24}{L} \alpha Q_{\text{max}} P(Z, E),$$

(12)
where $Q_{\text{max}} = 7000/6.24 \, \mu m^2 \, Gy$ for solid cancer and $Q_{\text{max}} = 1750/6.24 \, \mu m^2 \, Gy$ for leukemia.

Figure 3 shows the total REID% as a function of percent reduction of $Q_{\text{max}}$. Median values and 95% confidence intervals (CI) are in blue, and the point estimates are shown in green. The red dashed line indicates the NASA career radiation exposure limit for fatal cancer of 3% REID at the upper 95% CL. The 0% reduction is the total REID% for the mission with no MCM intervention. Results are also tabulated in Table 2. In addition to

![Graph showing total REID% as a function of percent reduction of $Q_{\text{max}}$. The red dashed line indicates the NASA career radiation exposure limit for fatal cancer of 3% REID at the upper 95% CL. The 0% reduction is the total REID% for the mission with no MCM intervention.](image)

Figure 3: Modifications of $Q_{\text{max}}$. A reduction of 67% of $Q_{\text{max}}$ for both solid cancer and leukemia is required to meet NASA PELS, which is indicated by the red dashed line.

In addition to the point estimates, medians, and confidence limits, Table 2 shows the average NASA quality factor, $\langle Q_{\text{NASA}} \rangle$, as computed for the lung,

$$\langle Q_{\text{NASA}} \rangle \approx \frac{H_{\text{lung}}}{D},$$

(13)

where $H_{\text{lung}}$ is dose equivalent for the lung and $D$ is the mission dose. The trend of the 95% CL is similar to that of the previous case. The cubic spline interpolation of the upper 95% CL in Appendix B shows that a 67% reduction is required to meet NASA PELS for fatal cancer.
Table 2: Modifications of $Q_{\text{max}}$

<table>
<thead>
<tr>
<th>Percent Reduction</th>
<th>Point Estimate</th>
<th>Median</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
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<tr>
<td>0</td>
<td>1.84</td>
<td>1.69</td>
<td>0.44</td>
<td>6.23</td>
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<tr>
<td>10</td>
<td>1.72</td>
<td>1.58</td>
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<td>20</td>
<td>1.6</td>
<td>1.47</td>
<td>0.39</td>
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<td>0.54</td>
<td>0.17</td>
<td>1.51</td>
<td>0.96</td>
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5.3 Background Cancer Mortality

Next, MCM modifications to the background cancer mortality rates for all cancers is considered. For this analysis, the sensitivity study treats MCM modifications completely independently of radiation induced cancer. The hazard rate from equation (3) must be considered carefully because of the underlying assumptions and unique characteristics of the NSCR. As seen in equation (3), the hazard rate is mixture of the ERR and EAR models. The NSCR uses ERR models based on cancer mortality, whereas the EAR models are based on cancer incidence (with the exception of BFO) and are converted to mortality rates by the scaling factor $R_T^M(a)$,

$$R_T^M(a) = \begin{cases} 
1 & \text{for BFO} \\
\frac{\lambda_{0,T}^M(a)}{\lambda_{0,T}^I(a)} & \text{otherwise,}
\end{cases}$$

where $M$ and $I$ represent mortality and incidence, respectively. Consequently, additional assumptions about how to scale incidence rates are required. Case 1 assumes that both cancer mortality and incidence rates may be scaled by $\alpha$:

$$R_T^{M\text{(Case1)}}(a) = \begin{cases} 
1 & \text{for BFO} \\
\frac{\alpha \lambda_{0,T}^M(a)}{\alpha \lambda_{0,T}^I(a)} & \text{otherwise.}
\end{cases}$$

where $M$ and $I$ represent mortality and incidence, respectively. Consequently, additional assumptions about how to scale incidence rates are required. Case 1 assumes that both cancer mortality and incidence rates may be scaled by $\alpha$:
This is interpreted as some MCM that reduces both cancer incidence and mortality commensurately.

Case 2 assumes that cancer mortality rates are scaled by factor $\alpha$, but the cancer incidence rates are unchanged; that is,

$$ R_{T}^{M(\text{Case 2})}(a) = \begin{cases} 1 & \text{for BFO} \\ \frac{\alpha \lambda_{0,T}^{M}(a)}{\lambda_{0,T}(a)} & \text{otherwise.} \end{cases} \quad (16) $$

The idea is that perhaps some MCM could reduce cancer death without affecting cancer incidence. This could be accomplished by enhanced screening and early treatment.

The background mortality rates will be modified by $\alpha$ in both cases,

$$ \lambda_{T}^{MCM}(a, a_{E}, \nu_{T}, H_{T}, \Delta_{T}) = \nu_{T}\text{ERR}_{T}(a, a_{E}, H_{T}, \Delta_{T})\alpha \lambda_{0,T}^{M}(a) + R_{T}^{M}(a)(1 - \nu_{T})\text{EAR}_{T}(a, a_{E}, H_{T}, \Delta_{T}). \quad (17) $$

Likewise, the conditional probability of survival of the background population must be modified to account for changes that result from reduced cancer mortality. The conditional probability of survival may be expressed as

$$ S_{0}^{MCM}(a|a_{E}) = \frac{e^{-M(a)}}{e^{-M(a_{E})}} = \frac{\frac{-\int_{0}^{a} \mu(t)dt}{e^{-\int_{0}^{a_{E}} \mu(t)dt}}} {\frac{-\int_{0}^{a_{E}} \mu(t)dt}{e^{-\int_{0}^{a_{E}} \mu(t)dt}}}, \quad (18) $$

where $\mu(t)$ is the all-cause mortality rate. If the MCM acts by mitigating cancer mortality rates, then the all-cause mortality rate should be adjusted accordingly by some factor, $\gamma$, which is assumed to be independent of age,

$$ S_{0}^{\gamma MCM}(a|a_{E}) = \frac{\frac{-\int_{0}^{a} \gamma \mu(t)dt}{e^{-\int_{0}^{a_{E}} \gamma \mu(t)dt}}} {\frac{-\int_{0}^{a_{E}} \gamma \mu(t)dt}{e^{-\int_{0}^{a_{E}} \gamma \mu(t)dt}}} = \frac{e^{-\gamma M(a)}}{e^{-\gamma M(a_{E})}} = \left[ \frac{e^{-M(a)}}{e^{-M(a_{E})}} \right]^{\gamma} \quad (19) $$

If $C_{F}$ is the female cancer mortality percentage for all cancers, then the modification factor may be expressed as $\gamma \approx 1 - (1 - \alpha)$, where $\alpha \in (0, 1]$. Note that there is no modification when $\alpha = 1$; maximum modification occurs as $\alpha \to 0$. 

10
5.3.1 Case 1:

The REID is evaluated for Case 1 using equation (15), the MCM hazard rate from equation (17), and the modified survival probability from equation (20). Figure 4 shows the total REID% as a function of percent reduction of cancer mortality. Median values and 95% confidence intervals (CI) are in blue, and the point estimates are shown in green. The red dashed line indicates the NASA career radiation exposure limit for fatal cancer of 3% REID at the upper 95% CL. The 0% reduction is the total REID% for the mission with no MCM intervention. Results are also tabulated in Table 3.

![Figure 4: Reduction of cancer mortality (Case 1). It is assumed that both cancer mortality and incidence rates may be scaled by $\alpha$. Reduction of cancer mortality rates alone is not sufficient to meet NASA PELS, which is shown with the red dashed line.](image)

Note that by reducing the background cancer mortality rate by 100%, the upper 95% CL remains well above the NASA PELS. This can be explained by examining the tissues that contribute the greatest to the total REID when the cancer mortality is reduced by approximately 100%. Figure 5 shows the contributions from the breast and lungs to the total REID for $\alpha = 0.001$. The NSCR uses only an EAR model for breast and a 50% mixture of the EAR and ERR models for the lungs. All other tissues use a mixture of 70% ERR and 30% EAR. Therefore, when the cancer mortality rate is reduced to approximately zero, the ERR term is no longer contributing, and upper 95% CL is being driven by the EAR models and sampled uncertainties. **In summary, a reduction of the background cancer mortality rates alone is not sufficient to meet NASA**
PELS.

Figure 5: The largest two contributors to the total REID when the reduction of the cancer mortality approaches 100% for background cancer mortality modifications (Case 1). The breast and lung distributions contribute significantly to the total REID, and the associated uncertainty results in a total REID where the upper 95% CL remains large.

5.3.2 Case 2:
The REID is evaluated for Case 2 using equation (16), the MCM hazard rate from equation (17), and the modified survival probability from equation (20). Figure 6 shows the total REID% as a function of percent reduction of cancer mortality. Median values and 95% confidence intervals (CI) are in blue, and the point estimates are shown in green. The red dashed line indicates the NASA career radiation exposure limit for fatal cancer of 3% REID at the upper 95% CL. The 0% reduction is the total REID% for the mission with no MCM intervention. Results are also tabulated in Table 4.

As described above, this case is associated with mitigation of cancer deaths but with no change to cancer incidence. With this assumption, the total REID decreases as a function of percent reduction, as expected. Cubic spline interpolation of the upper 95% CL found in Appendix B shows that a 57% reduction is needed to meet NASA PELS. However, these results are a consequence of the unique way in which the NSCR scales incidence based EAR models for most tissues to mortality based EAR models that are
required for estimation of the REID. If EAR models were based only on mortality data, then these results would not be valid.

6 Summary

The impact of modifying the low-LET risk model coefficients, the high-LET component of the NASA quality factor ($Q_{\text{max}}$), and the cancer mortality rates were studied in this sensitivity analysis. For the purposes of this study, each was treated independently. For example, any modifications to the background cancer mortality rates were assumed to have no impact on radiation risk models. Likewise, MCM modification of the high-LET component of the NASA quality factor is assumed to act through some pathway that mitigates the biological response to heavy ions only.

The results show that mitigation of the biological impacts of both low-LET and high-LET radiation have the greatest impact on space radiation risk reduction. Although this study has proceeded with no assumed interdependence, it is likely that commensurate reductions to both low-LET and high-LET radiation would have an even more significant reduction in risk. The study showed that modification of background cancer mortality rates (Case 1) alone is not sufficient to meet NASA PELS. However, it should be noted that this is the consequence of the NSCR model’s mixture of ERR and EAR models. Since background cancer mortality rates multiply the ERR, the total hazard rate may
Figure 6: Reduction of cancer mortality (Case 2). It is assumed cancer mortality rates are scaled by factor $\alpha$, but the cancer incidence rates are unchanged. Although it is shown that a 57% reduction is required to meet NASA PELS, indicated with the red dashed line, this result is a consequence of the unique way in which the NSCR scales cancer incidence based EAR models to cancer mortality based EAR models that are required for estimation of the REID.
also receive contributions from the EAR models for certain tissues (for example, lung and breast in the NSCR model), even when the cancer mortality rates are scaled to zero. Therefore, the uncertainties of the EAR model are large enough that the upper 95% CL of the REID is not significantly reduced. Finally, the NSCR uses a unique procedure where cancer incidence based EAR models are scaled to mortality based EAR models for most tissues. Given that the REID is evaluated from cancer mortality hazard rates, interpretation of these results of cancer mortality modification (Case 2) is difficult and may be easily misinterpreted. Finally, it should be noted that various other Mars mission scenarios may be studied; however, the qualitative results will remain unchanged. Next, the core findings of this study are stated concisely.

- MCM modification of low-LET risk model coefficients
  - 55% reduction is required to meet NASA PELS for fatal cancer
- MCM modification of high-LET component of NASA Quality factor model ($Q_{\text{max}}$)
  - 67% reduction is required to meet NASA PELS for fatal cancer
- MCM modification of the background cancer mortality rates

<table>
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<th>Percent Reduction</th>
<th>Point Estimate</th>
<th>Median</th>
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<th>Upper 95% CL</th>
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</table>
A reduction of the cancer mortality rates alone is not sufficient to meet NASA PELS for fatal cancer

Appendix A. Review of low-LET risk models

The NSCR model uses excess relative risk (ERR) and excess absolute risk (EAR) for comparisons of disease rates between exposed and unexposed cohorts. The ERR is expressed in terms of the relative risk (RR) of the exposed disease rate (DR_E) to the non-exposed disease rate (DR_NE) [12]

\[
\text{ERR} \equiv [\text{RR} - 1] \frac{1}{D} = \left[ \frac{\text{DR}_E}{\text{DR}_\text{NE}} - 1 \right] \frac{1}{D},
\]

where D is the average dose of the exposed group. The EAR is the difference of the absolute risks,

\[
\text{EAR} = [\text{DR}_E - \text{DR}_\text{NE}] \frac{D}{\text{PY}},
\]

where PY is the number of person years.

Table 5 shows a cohort of size N where individuals in sub-cohorts A and B were exposed to radiation, and those in sub-cohorts C and D were not exposed to radiation. Sub-cohorts A and C are in the diseased state; B and D are not diseased. Therefore, the disease rates are

\[
\text{DR}_E = \frac{A}{A + B} \quad \text{DR}_\text{NE} = \frac{C}{C + D}.
\]

Table 5: Disease table for a cohort of size N (adapted from [12]).

<table>
<thead>
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<th>Exposure</th>
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<th>NO</th>
<th>TOTAL</th>
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<td>B</td>
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<tr>
<td>NO</td>
<td>C</td>
<td>D</td>
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<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
<td>N</td>
</tr>
</tbody>
</table>

The ERR is proportional to the background disease rate of the cohort without radiation exposure, \( \lambda_0 \), and the risk is expressed as

\[
R_{\text{ERR}} = [1 + \text{ERR}(D, \epsilon)]\lambda_0(\delta).
\]

The \( \epsilon \) and \( \delta \) represent sex, age, age of exposure, city, and many other possible factors that may have an impact on the disease rates. The risk may also be expressed as an excess
that is not proportional to the background, $\lambda_0$,

$$R_{\text{EAR}} = \lambda_0(\delta) + \text{EAR}(D, \epsilon). \quad (25)$$

The ERR and EAR models in the NSCR are assembled from the Japanese atomic bomb cohort. The NSCR accounts for uncertain knowledge of the how to transfer the risk from the Japanese to the US cohort, in part, by assigning risk transfer weighting factors. The tissue specific low-LET models and weighting factors are described in Cucinotta et al. [3].

**Appendix B. Interpolation Results**

This section shows the cubic spline interpolation of the upper 95% CL for the low-LET model modifications in Figure 7, $Q_{\text{max}}$ modifications in Figure 8, and modifications to cancer mortality rates (case 2) in Figure 9.

![Cubic Spline Interpolation](image)

**Figure 7:** Reduction of upper 95% CL (low-LET risk model modifications).
Figure 8: Reduction of upper 95% CL ($Q_{\text{NASA}}$ modifications.)

Figure 9: Reduction of upper 95% CL (background mortality modifications.)
References


The space radiation environment consists of ionizing radiation that poses health risks to crew members who embark on a mission to Mars. NASA requires that astronaut career radiation limits for the Risk of Exposure Induced Death should not exceed 3% at the upper 95% confidence level for cancer mortality. However, the lifetime career limit is likely to be exceeded for even the shortest round-trip mission scenario to Mars. The present work addresses the general medical countermeasure requirements that are needed to meet the lifetime career exposure limits by examining modifications to the background cancer mortality rates, radiation quality factor, and low-LET radiation risk models for a Mars mission scenario.