MIND THE GAP: EXPLORING THE UNDERGROUND OF THE NASA SPACE CANCER RISK MODEL

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Goal

To combine research aims and the current NASA Space Cancer Risk (NSCR) 2012 model into an illustrative allegory.

Background

As one of the many risks inherent to space travel, radiation exposure over an astronaut's career is limited by the space permissible exposure limit (SPEL). This limit is defined in the NASA Standard 3001 [1] which states: *Planned career exposure to ionizing radiation shall not exceed three percent Risk of Exposure-Induced Death (REID) for cancer mortality at a 95 percent confidence level*. The REID quantifies the lifetime risk of death from radiation-induced cancer in an exposed astronaut. The NASA Space Cancer Risk (NSCR) 2012 model [2] incorporates elements from physics, biology, epidemiology, and statistics to generate the REID distribution. The current model quantifies the space radiation environment, radiation quality, and dose-rate effects to estimate a NASA weighted dose. This weighted dose is mapped to the excess risk of radiation-induced cancer mortality from acute exposures to gamma rays and then transferred to an astronaut population. Finally, the REID is determined by integrating this risk over the individual's expected lifetime. The calculated upper bound of the 95% confidence interval of the REID is used to restrict an astronaut's permissible mission duration (PMD) for a proposed mission. As a statistical quantity characterized by broad, subjective uncertainties, probabilistic assessments of REID for space missions result in wide distributions. Currently, the upper 95% confidence level is over 350% larger than the mean REID value, which can severely limit an astronaut's PMD.

The model incorporates inputs from multiple scientific disciplines in the risk estimation process. Physics and particle transport models calculate how radiation moves through space, penetrates spacecraft, and makes its way to the human beings onboard. Epidemiological studies of exposures from atomic bombs, medical treatments, nuclear materials, etc. are used to quantify health risks from acute and chronic low linear energy transfer (LET) ionizing radiation. Biological studies in cellular and animal models using radiation at various LETs and energies inform quality metrics for ions present in space radiation. Statistical methodologies unite these elements, controlling for mathematical and scientific uncertainty and variability. Despite current progress, these research platforms contain knowledge gaps contributing to the large uncertainties still present in the model. The NASA Space Radiation Program Element (SRPE) defines the *knowledge gaps* that impact our understanding of cancer risks. These gaps are outlined in NASA's Human Research Roadmap [3], which identifies the research questions and actions recommended for reducing the uncertainty in the current NSCR model and for formulation of future models.

The greatest contributors to uncertainty in the current model include radiation quality, low dose and dose-rate effects, and the transfer of exposure-based risk from other populations to an astronaut population. Here, we discuss the current capabilities of the NSCR-2012 model and several immediate research needs, highlighting areas expected to have an operational impact on the current model schema.

NASA Quality Factor Function

As demonstrated in the subway style map to the right, the NASA Quality Factor Function is the current mechanism that relates the biological effects of sparsely ionizing (low LET) to densely ionizing (high LET) radiation. The current function parameterizes a risk cross section that approximates the track-structure models originating from Katz [4]. This function only incorporates track structure differences between ions with no integration of biological mechanisms. Ideally, human epidemiology data would provide a method to assimilate the biological mechanisms which modify the physical attributes of the energy deposition spectrum. However, only sparse data exists regarding the effects of high LET radiation on humans. It is therefore necessary to incorporate research findings from animal and cellular experiments into models of radiation quality. Gap 3 highlights the research required to better understand the differences between the varying qualities of radiation in space.

DDREF

The Dose and Dose Rate Effectiveness Factor (DDREF) scales high doses and acute dose rates to low doses and chronic dose rates. The DDREF should be characterized by a wide uncertainty distribution to reflect the ongoing debate in the radiation community of a good estimate for this scaling factor. The uncertainty is complicated by the correlation between the dose rate and radiation quality effects. Gap 4 corresponds to research questions focused on low dose, fractionated, and chronic exposures. It is important that current research includes exposures that are relevant to those experienced in space, both in dose level as well as dose rate. Fractionated exposures may not be an appropriate surrogate for the biological response to true low dose-rate protracted exposures. Furthermore, while measurements at low doses and dose rates are important, high dose exposures must be recorded as well to enable the calculation of the DDREF metric. The SPRE's Gaseous Core Reactor (GCR) simulator experimental consortium is currently focused on developing the infrastructure required to successfully address these issues.

Conclusions

The current NSCR 2012 model relies heavily on epidemiology data for risk estimation. With the current model formulation the most impactful areas of research include those that inform the radiation quality factor and DDREF. As shown by the monorail of radiation research, incorporation of new research findings in these areas into the space radiation cancer risk model is a high priority of the SRPE and is required for successful construction of the research connector services (dashed purple lines) depicted on the subway map.

References

[1] *NASA Technical Standard, NASA-STD-3001, Vol. 1, Revision A*.

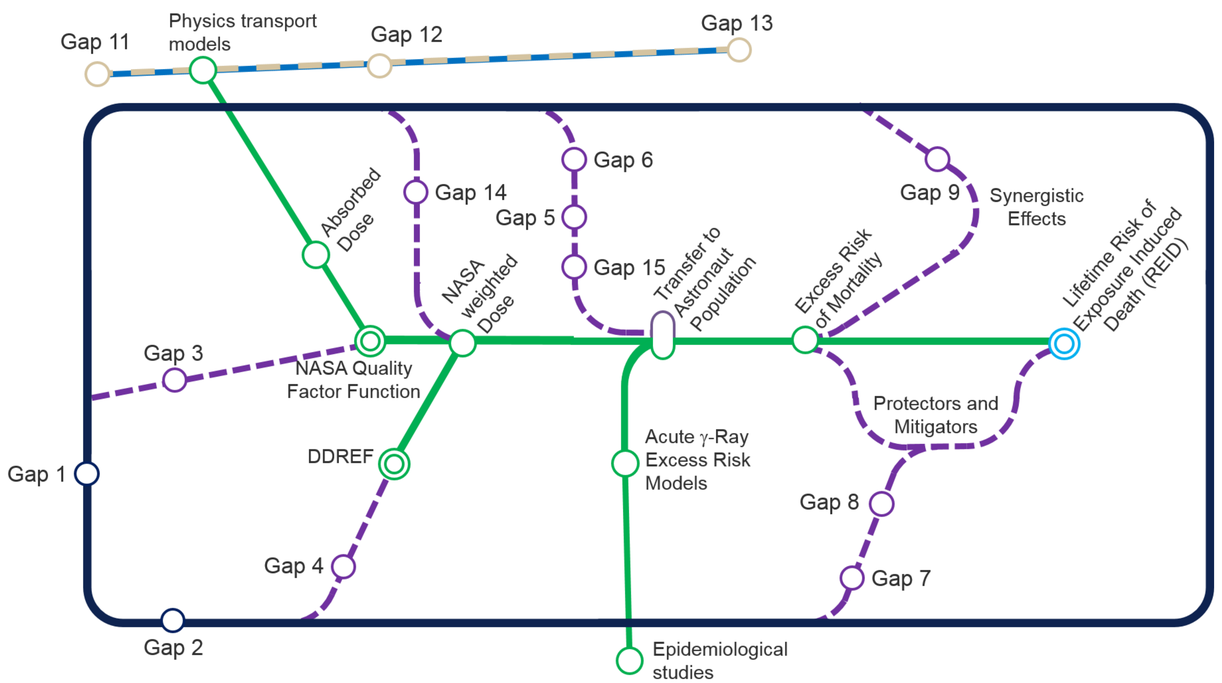
[2] Cucinotta F.A., Kim M.Y., and Chappell L.J. (2013) *NASA JSC TP 2013-217375*.

[3] NASA HRP (2016) *https://humanresearchroadmap.nasa.gov/Risks/risk.aspx?i=96*. Accessed Oct 26 2016.

[4] Katz R., Ackerson B., Homayoonfar M. (1971) Rad Res 47:402-425.

[5] Attix, F.H. (2004) *Introduction to Radiological Physics and Radiation Dosimetry.* Wiley-VCH. *p* 27.

Subway-style notional map featuring the NSCR-2012 model



Map Key

- The NSCR-2012 model – Incorporates elements from physics, biology, epidemiology, and statistics to generate the REID.
- Physics transport models – Calculate how radiation moves through space, penetrates spacecraft, and makes its way to the human beings onboard.
- Absorbed Dose – "The expectation value of the energy imparted to matter per unit mass at a point."[5]
- NASA Quality Factor Function – A function that relates the biological effects of sparsely to densely ionizing radiation.
- DDREF – A scaling factor that relates the biological effects of high dose acute radiation exposures to low dose chronic exposures.
- NASA weighted Dose – A dose quantity calculated for individual organs/tissues derived from the absorbed dose and modified to reflect differences in radiation quality using the NASA Quality Factor Function.
- Epidemiological studies – Exposures from the atomic bombings, medical treatments, nuclear material workers, etc. are used to quantify health risks from acute and chronic low LET ionizing radiation.
- Acute γ-Ray Excess Risk Models – Excess Relative Risk (ERR) and Excess Absolute Risk (EAR) parameters estimated using epidemiological studies.
- Transfer to Astronaut Population – The excess risk from epidemiological studies is transferred additively or multiplicatively to a population more representative of NASA Astronauts.
- Excess Risk of Mortality – The risk of cancer mortality above the baseline risk at each age.
- Lifetime Risk of Exposure Induced Death (REID) – The excess risk of mortality integrated over the individual's expected lifetime.
- Monorail of Radiation Research – Ground-based, peer-reviewed research using state of the art cell and animal models along with acquisition of *'omics'* datasets will be conducted to reduce uncertainty in the current cancer risk model and more accurately quantify radiation cancer risk. Serves as the basis to bridge gaps included in the research connector service to the NSCR-2012 model.
- Research connector service – Models and/or mechanisms to connect the biological research to the radiation risk model. Currently under construction.
- Physics express train – Research using state of the art detectors and models to describe the physical attributes of the ionizing radiation environment and its interaction with matter.

- Gap 1 – Establish mechanisms of space radiation induced cancer initiation, promotion and progression for the highest risk tissues (lung, colon, stomach, breast, liver, and blood forming organs).
- Gap 2 – Ascertain the mechanisms of space radiation induced cancer initiation, promotion and progression for the minor tissue sites (bladder, ovary, brain, esophagus, skin, etc.).
- Gap 3 – Define the impact of radiation quality on cancer development processes and determine whether or not heavy ion effects can be scaled to gamma rays.
- Gap 4 – Estimate low dose and dose rate effects for protons, heavy ions and secondary neutrons.
- Gap 5 – Understand how genetic and epigenetic factors influence radiation sensitivity.
- Gap 6 – Assess the impact of age and sex specific dependence on space radiation carcinogenesis.
- Gap 7 – Integrate large 'omics' datasets into next generation cancer risk models using system biology approaches to improve predictions and evaluate countermeasures.
- Gap 8 – Evaluate the most effective biomedical or dietary countermeasures to mitigate cancer risks due to space radiation exposure.
- Gap 9 – Recognize whether other spaceflight factors (e.g. altered gravity, stress, altered immune function, altered circadian rhythms, depressed nutritional status) modify the carcinogenic risk from space radiation.
- Gap 10—Validation experiments (not represented in diagram).
- Gap 11 – Calculate the most effective shielding approaches to mitigate cancer risks.
- Gap 12 – Describe the primary space radiation environment and transport through spacecraft materials and tissue, evaluating dose composition in critical organs for mission relevant radiation environments.
- Gap 13 – Develop an integrated radiation design and analysis tool compliant with NASA Standards and accessible to the engineering community.
- Gap 14 – Identify biodosimetry methods and biomarkers to determine individual radiation susceptibility for early detection of adverse radiation induced health outcomes.
- Gap 15 – Determine possible interactions between radiation and tobacco products.