Estimation of the Dose and Dose Rate Effectiveness Factor
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Summary
Current models to estimate radiation risk use the Life Span Study (LSS) cohort that received high doses and high dose rates of radiation. Transferring risks from these high dose rates to the low doses and dose rates received by astronauts in space is a source of uncertainty in our risk calculations. The solid cancer models recommended by BEIR VII [1], UNSCEAR [2], and Preston et al [3] is fitted adequately by a linear dose response model, which implies that low doses and dose rates would be estimated the same as high doses and dose rates. However animal and cell experiments imply there should be curvature in the dose response curve for tumor induction. Furthermore animal experiments that directly compare acute to chronic exposures show lower increases in tumor induction than acute exposures. A dose and dose rate effectiveness factor (DREF) has been estimated and applied to transfer risks from the high dose and dose rates of the LSS cohort to low doses and dose rates such as from missions in space.

The BEIR VII committee [1] combined DOREF estimates using the LSS cohort and animal experiments using Bayesian methods for their recommendation for a DOREF value of 2.5 with uncertainty. We reexamined the animal data considered by BEIR VII and included more animal data and human chromosome aberration data to improve the estimate of DOREF. Several experiments chosen by BEIR VII were deemed inappropriate for application to human risk models of solid cancer risk. Animal tumor experiments performed by Ullrich et al [4], Alpen et al [5], and Grahn et al [6] were to estimate the DOREF. Human chromosome aberration experiments performed on a sample of astronauts within NASA were also available to estimate the DOREF. The LSS cohort results reported by BEIR VII were combined with the new radiobiology results using Bayesian methods.

Estimate the likelihood of the LSS Cohort using BEIR VII reported values
A log-normal distribution was fit using the reported LSS DOREF and confidence limit.

Reexamine the animal tumor data considered by BEIR
We reanalyzed the animal experiments performed by Ullrich et al [4] and added the tumor data published by Alpen et al [5] for the Pituitary gland. Only doses below 2 Gy were included in the analysis. We analyzed all the data jointly assuming that the curvature, \( \theta \), was the same for all tumor types. The model allows each type of cancer and type of mouse to have its own baseline cancer risk, linear increase, and quadratic increase in cancer risk. Unlike the BEIR VII analysis, we allowed the chronic data to contribute to the estimation of the linear term in the model. The curvature is estimated instead of the quadratic term as follows:

\[
Risk = c_i + a_i [Dose + \theta Dose^2] \cdot I(Dose_{acute})
\]

where \( c_i \) is an indicator for each type of cancer and mouse and \( I(Dose_{acute}) \) is the indicator function for acute doses. The model assumes risks are normally distributed with variances that are proportional to the reciprocal of the squared standard errors. We assumed that the DOREF has a log-normal distribution with mean \( 1 + \theta \) and variance determined using the delta method.

Combine the Distributions using Bayesian methods
Each prior distribution and likelihood is assumed to be log-normal. Using a conjugate prior determined by the log-normal distributions, combining these distributions results in a posterior with a student’s t-distribution on the log scale.

Results
Results are based on a Bayesian statistical analysis of DOREF values. The probability density labeled “Astronaut CA” expresses the belief about DOREF deduced from human chromosome aberration experiments performed on a sample of astronauts within NASA. The probability density labeled “Animal Cancer Risks” expresses the belief about DOREF deduced from animal tumor experiments performed by Ullrich et al [4] and Alpen et al [5]. The probability density labeled “Argonne Lab Animals” expresses the belief about DOREF deduced from animal tumor experiments performed by Grahn et al [6]. The probability density labeled “LSS cohort” expresses the belief about DOREF approximated from the BEIR VII reported LSS data [1]. The “combined” density is the Bayesian posterior obtained by updating the radiobiological densities to account for the information from the LSS data.

References

Incorporate the Astronaut chromosome aberation data
The chromosome aberation data were combined similarly to the animal cancer risk data for 28 individual astronauts. Translocations were used as the measure of chromosome damage using 3 color FISH [5].

\[
Risk = c_i + a_i [Dose + \theta Dose^2]
\]

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Incorporate the Argonne National Lab animal data
Grahn et al [6] published analyses of survival data for mice exposed acutely and chronically which included histological tumor information for the causes of death. Linear dose response, \( \alpha \)-values were published for both the acute and chronic data. The data were divided into individual epithelial cancers which included lung, liver, Harderian gland, and glandular/reproductive tumors. The data were further divided by gender and into two intervals of ages, 60-79 days and 800-799 days. For each cancer type, gender and age interval, the DOREF can be estimated using the published \( \alpha \)-values as follows:

\[
\text{DREF} = \frac{\alpha_{acute}}{\alpha_{chronic}}
\]

If we assume that the DOREF is log-normal, we can estimate the variance of the natural log of the DOREF as:

\[
\text{Var}(\ln(\text{DREF})) = \frac{SE_{\alpha_{chronic}}^2}{\alpha_{chronic}^2} + \frac{SE_{\alpha_{acute}}^2}{\alpha_{acute}^2}
\]

The natural logarithm transformed DOREF’s can be aggregated across the different cancer types, genders, and age intervals using the generalized inverse variance method.

References