



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 (DDREF) has been estimated and applied to transfer risks from the high doses 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 DDREF estimates using the LSS cohort and animal experiments using Bayesian methods for their recommendation for a DDREF value of 1.5 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 for DDREF. 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 Grahm et al [6] were analyzed to estimate the DDREF. Human chromosome aberration experiments performed on a sample of astronauts within NASA were also available to estimate the DDREF. 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

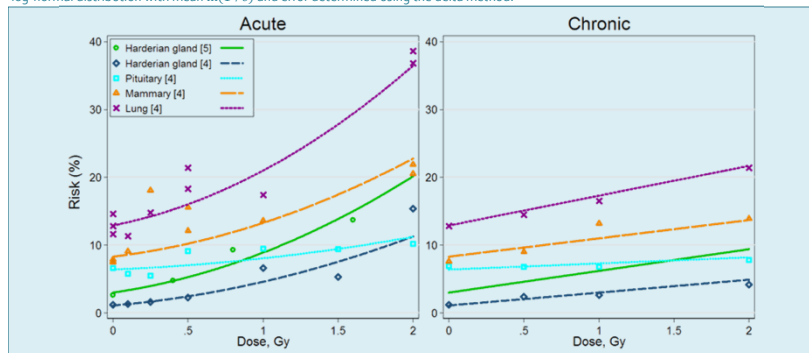
A log-normal distribution was fit using the reported LSS DDREF and confidence limit.

Reexamine the animal tumor data considered by BEIR

We reanalyzed the animal tumor 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 2Gy were included in the analysis. We analyzed all the data jointly assuming that the curvature, θ , 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:

$$Risk = c_i + \alpha_i [Dose + \theta Dose^2 \times I(Dose_{acute})]$$

where 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 DDREF has a log-normal distribution with mean $\ln(1+\theta)$ and error determined using the delta method.



Incorporate the Argonne National Lab animal data

Grahm 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, α 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, 600-799 days and 800-899 days. For each cancer type, gender and age interval, the DDREF can be estimated using the published α values as follows:

$$DDREF = \frac{\alpha_{acute}}{\alpha_{chronic}}$$

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

$$Var(\ln(DDREF)) = \left(\frac{SE_{chronic}}{\alpha_{chronic}} \right)^2 + \left(\frac{SE_{acute}}{\alpha_{acute}} \right)^2$$

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

References

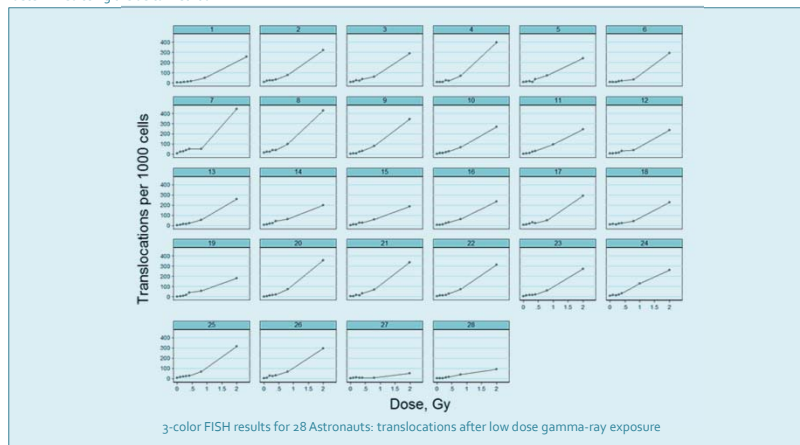
- [1] National Academy of Sciences Committee on the Biological Effects of Radiation (2006) BEIR VII.
- [2] Preston D.L. et al (2007) *Radiat Res* 168, 1-64.
- [3] Alpen E.L et al (1993) *Radiat Res* 136, 382-391.
- [4] George K, Cucinotta FA (2006) *Adv Space Res*.

Incorporate the Astronaut chromosome aberration data

The chromosome aberration 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 [7]. Each astronaut in the model had their own estimate for initial prevalence and linear increase. The combined curvature, θ , in the linear quadratic fit for astronaut translocation could be determined as:

$$Risk = c_i + \alpha_i [Dose + \theta Dose^2]$$

Only doses below 2.5 Gy were included in the analysis. The model assumes risks are normally distributed with variances that are proportional to the reciprocal of the squared standard errors. We assumed that the DDREF had a log-normal distribution with mean $\ln(1+\theta)$ and error determined using the delta method.



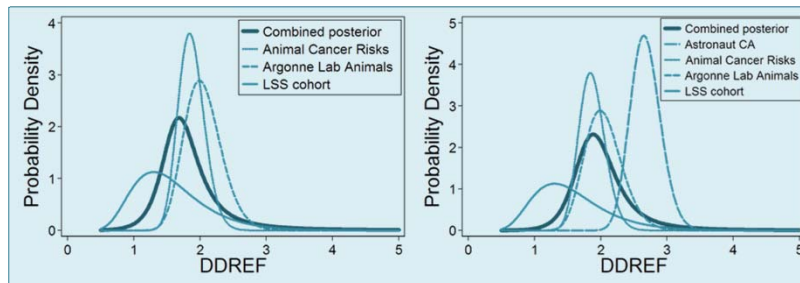
Combine the Distributions using Bayesian methods

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 DDREF values. The probability density labeled "Astronaut CA" expresses the belief about DDREF 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 DDREF deduced from animal tumor experiments performed by Ullrich [4] and Alpen [5]. The probability density labeled "Argonne Lab Animals" expresses the belief about DDREF deduced from animal tumor experiments performed by Grahm [6]. The probability density labeled "LSS cohort" expresses the belief about DDREF 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.

	Estimated DDREF
LSS cohort	1.3 (0.8, 2.6)
Animal Cancer Risks	1.84 (1.49, 2.27)
Argonne Lab Animals	1.99 (1.52, 2.61)
Astronaut CA	2.65 (2.24, 3.13)
Posterior: BEIR VII	1.5 (1.1, 2.6)
Posterior: LSS + animal	1.7 (1.0, 2.9)
Posterior: all	1.9 (1.2, 3.0)



- [2] United Nations Scientific Committee on Effects of Atomic Radiation (2008) UNSCEAR 2006 Report to the General Assembly.
- [4] Ullrich R.L. and Storer J.B. (1979) *Radiat Res* 80, 325-342.
- [6] Grahm D. et al (1992) *Radiat Res* 129, 19-36.