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Institution: Medical University of South Carolina

Title: Radiation Leukemogenesis: Applying Basic Science to Epidemiological Estimates of Low Dose Risks and Dose-Rate Effects

SC Division: SC-72

Program Manager: Arthur M. Katz 301-903-4932

Research Areas: Low Dose

Final Technical Report

Most recent report of results to date:

Summary of New Results

The work on Aims 1 and 2 is essentially completed. The basic manuscript, "Biologically-Based Risk Estimation for Radiation-Induced Chronic Myeloid Leukemia" by Radivoyevitch and Hoel Radiat. Environ Biophysics 39:153-159 (2000)

The next stage of work has been to examine more closely the A-bomb leukemia data which provides the underpinnings of the risk estimation of CML in the above mentioned manuscript. The paper by Hoel and Li (Health Physics 75:241-50)shows how the linear-quadratic model has basic non-linearities at the low dose region for the leukemias including CML. Pierce et. al., (Radiation Research 123:275-84) have developed distributions for the uncertainty in the estimated exposures of the A-bomb cohort. Kellerer, et. al., (Radiation and Environmental Biophysics 36:73-83) has further considered possible errors in the estimated neutron values and with changing RBE values with dose and has hypothesized that the tumor response due to gamma may not be linear. We have incorporated his neutron model and have constricted new A-bomb doses based on his model adjustments. The Hoel and Li dose response analysis has also been applied using the Kellerer neutron dose adjustments for the leukemias. Finally, both Pierce's dose uncertainties and Kellerer neutron adjustments are combined as well as the varying RBE with dose as suggested by Rossi and Zaider and used for leukemia dose-response analysis. First the results of Hoel and Li showing a significantly improved fit of the linear-quadratic dose response by the inclusion of a threshold (i.e. low-dose nonlinearity) persisted. This work has been complete for both solid tumor as well as leukemia for both mortality as well as incidence data. The results are given in the manuscript described below which has been submitted to Health Physics.

The approach we are using is the two-stage birth/death mutation model as developed by Moolgavkar and generalized by others. This model has been programmed using maximum likelihood methods and analyses have begun. First there are questions of parameter identifiability. A manuscript on a solution to this issue as it applies to our radiation cancer models is under journal review. We have been collaborating with Doug Grahn, Peter Groer and Bruce Carnes with respect to the Argonne dose rate and radiation type mouse studies referred to as the Janus Program. We have applied the biologically based two stage model to this mouse data using total tumors. Good results have been shown for dose rate effects with both gamma and neutron exposures. A clear dose-rate effect is seen for mean time to tumor for gamma exposures but not for neutron. We next are using specific cancer type and expect that what we find for hematopoietic tumors in the mouse will be relevant. Besides dose-rate and RBE we examined the data to see if any similar non-linearities at low dose are present as with the A-bomb data. This work has been completed for lymphoreticular cancers as well as total solid tumors. The results have been submitted in two mauscripts described below.

Next we intend to look at specific tumor types. Also we will examine more closely the DREF results for both lymphoreticular cancers and solid cancers.

Most recent products delivered:

Papers submitted or published:

#4 Biologically-Based Risk Estimation for Radiation-Induced Chronic Myeloid Leukemia was published in Radiation & Environmental Biophysics 39:153-159, 2000.

#7 Conditional Likelihood for Two-Stage Model with Application to Cancer incidence Data.

T. Nakamura and D. G. Hoel

Risk Analysis (submitted)

This is a methods paper which provides a computing algorithum for estimating the maximum likelihood parameters in a biologically based two-stage cancer model. The algorithm was used to estimate the model for the Argonne Laboratory mouse studies using gamma and neutron exposures.

#8
The Risk of Chronic Myeloid Leukemia: Can the Dose-Response Curve be U-Shaped? T. Radivoyevitch, S. Kozubek, and R.K. Sachs
Radiation Research 157 106-109 (2002)

#9
Two-Stage Cancer Models Applied to Gamma and Neutron Exposed Mice
G. Tessier, C. Lam, T. Nakamura and D.G. Hoel
European Journal of Oncology 6:297-301 (2001)

#10
Comparing Risks between Radiation and Dioxin Exposure Based on Two-Stage model. T. Yanagawa and D. Hoel
Econometrics 2002 (to appear)

The two-stage cancer model was fit to whole animal liver cancer data from Dioxin exposure. The model indicated that the proliferation rate for initiated cells was increased by about 30%, which agreed with initiation promotion models of liver foci (DEN and TCDD). The gamma exposed mice showed and increase in iniation only without the proliferation effect.

#11
Corrections in the Atomic bomb data to examine low dose risk.
G. Baker and D. Hoel
Health Physics (submitted)
Cancer incidence and mortality data from the cohort of Japanese atomic bomb survivors has been adjusted for uncertainty that exists in the dose estimates, systematic error in the neutron dose estimates, and a dose-dependent relative biological effectiveness. Once the adjustments were incorporated in the dose estimates the data was analyzed to allow for the possibility of a threshold dose response. The dose response models that were fit to the data were the same models used in the original papers. A threshold term was included in the model with possible threshold values ranging from 0 to 0.35 Sv. These analyses suggest that for the A-bomb solid tumor and leukemia incidence data a threshold term significantly improves the fit to the purely linear or linear quadratic model. The results from the mortality data suggests that the leukemia data agree more with the threshold model than the linear quadratic model although the linear quadratic model is statistically equivalent, while the solid tumor data does not suggest any improvement with a threshold.

#12
Comparison of Two Models of Risk Estimation Part I: Low Dose Region.
Radiat.Research (submitted)
G. Baker, T. Nakamura and D. Hoel
A low dose subset of experimental mortality data from experiments conducted at the Argonne National Laboratory on the effects of exposure of B6CF1 mice to whole-body irradiation, gamma rays (< 300cGy) or fission neutrons (< 30cGy), were analyzed to assess the shape of the dose response and the effects of fractionation. The Cox proportional hazards model was used as an empirical model, while the two-stage clonal expansion model was used as the biologically based cancer model in which information on the carcinogenesis process is

incorporated into the model. The two models resulted in similar descriptions of the dose response curves, cancer risks, neutron relative biological effectiveness and dose rate effectiveness factor associated with exposure to ionizing radiation. Both models suggest that a dose-response curve linear in dose provides an adequate fit to the data. Fractionation reduced the effectiveness of gamma radiation while had no noticeable impact on the effectiveness of neutron exposure.

#13
Comparison of Two Models of Risk Estimation Part II: Entire Dose Range.
G. Baker, T. Nakamura and D. Hoel
Radiat. Research (submitted)

The analyses in this paper are based on an expanded subset of the experimental mortality data used in Part I.

Most recent notes concerning the project:

Last year the uncertainties in dosimetry in the A-bomb studies were discussed. The calculations of new adjusted doses for the A-bomb survivors has been more complex than previously thought. We do now have the new adjusted doses as well as a new method for estimating the uncertainty in these adjusted doses. The leukemia and solid tumor dose response models have been recalculated using these adjusted doses and show that the previous finding of a threshold like response persists for leukemia.

Using the individual mouse data as contrasted with grouped data from the Argonne Laboratory Janus program, two-stage cancer model parameters have been estimated for total tumor, hematopoietic tumors, epithelial tumors and connective tissue tumors. The parameters are for various dose levels of gamma and neutron as well as acute and fractionated exposures. These parameter estimates have been analyzed to assess the general effects of radiation type and dose-rate on the broad cancer type groupings.
The A-bomb cancer dose-response models were redone after the incorporation of factors effect the dosimetry. In particular 1) exposure uncertainty was incorporated, 2) Errors in the estimated fast neutron values were accounted for, 3) the variable neutron RBE which varies with dose as suggested by Rossi and Zaider was included. The dose-response for both cancer incidence as well as cancer mortality was then calculated for leukemia and for solid tumors. For leukemia and the linear-quadratic model both incidence and mortality was significantly improved with the incorporation of a threshold at about 0.1 Sv. For solid tumors and a linear dose-response function the incorporation of a threshold improved the fit to the incidence data but not the mortality data.

The Argonne Janus mouse data has been modelled using both the Cox proportional hazard as well as the two-stage cancer model of Moolgavkar. The end points used were solid tumors and lymphoreticular cancers. Both RBE and

DREF were estimated using acute and 60 once weakly fractionated exposures. For solid tumors the RBE values were about 23 and DREF of 1.5 for gamma and 0.7 for neutron. For lymphoreticular cancers the RBE was 1.5 and DREF of 3.6 to 5.8 for gamma and 0.2-0.3 for neutron.

Experimental groups in the Argonne study included low doses of neutron (1,2,5 and 10 cGy). The cancer dose response was quite linear over these values as well as higher exposure values. This is interesting in that the proposed bystander effect based on alpha exposure would suggest non-linearity for neutron at these dose levels. Another observation with this mouse data is that the lower neutron doses showed no lymphoreticular effects but they did at doses 30 cGy.

Other Project Information Sources:

Project URL: None

Related URL at institution:

None