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Risk Analysis: Divergent Models and Convergent Interpretations

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Material presented at a NASA-sponsored workshop on risk models for exposure conditions relevant to prolonged space flight are described in this paper. Analyses used mortality data from experiments conducted at Argonne National Laboratory on the long-term effects of external whole-body irradiation on B6CF$_1$ mice by ^{60}Co γ rays and fission neutrons delivered as a single exposure or protracted over either 24 or 60 once-weekly exposures. The maximum dose considered was restricted to 1 Gy for neutrons and 10 Gy for γ rays. Proportional hazard models were used to investigate the shape of the dose response at these lower doses for deaths caused by solid-tissue tumors and tumors of either connective or epithelial tissue origin. For protracted exposures, a significant mortality effect was detected at a neutron dose of 14 cGy and a γ-ray dose of 3 Gy. For single exposures, radiation-induced mortality for neutrons also occurred within the range of 10–20 cGy, but dropped to 86 cGy for γ rays. Plots of risk relative to control estimated for each observed dose gave a visual impression of nonlinearity for both neutrons and γ rays. At least for solid-tissue tumors, male and female mortality was nearly identical for γ-ray exposures, but mortality risks for females were higher than for males for neutron exposures. As expected, protracting the γ-ray dose reduced mortality risks. Although curvature consistent with that observed visually could be detected by a model parameterized to detect curvature, a relative risk term containing only a simple term for total dose was usually sufficient to describe the dose response. Although detectable mortality for the three pathology end points considered typically occurred at the same level of dose, the highest risks were almost always associated with deaths caused by tumors of epithelial tissue origin.

INTRODUCTION

''It does not matter whether the cat is white or black, it only matters if the cat can catch mice.''

—Deng Xiaoping

Space exploration by humans will increase in the future, the radiation environment in space is complex, and exposure to radiation has known adverse health consequences. These realities make the identification and quantification of radiation-induced health risks important objectives in research funded by NASA. Several obstacles complicate the task of achieving these objectives. First among these is the fact that NASA must minimize health risks for humans, but there are only limited data available for the direct measurement of radiation effects in humans. In addition, the data that are available for humans lack the energy spectrum and patterns of exposure that are most relevant to the radiation environment in space. One way to circumvent this problem is to use the wealth of data that exist for radiation effects observed in laboratory animals. This approach, however, requires demonstrating that it is possible to make reasonable interspecies predictions of radiation-induced mortality risks (e.g. refs. *1, 2*).

Interspecies predictions are complicated not only by issues of biological comparability, but also by conceptual and quantitative modeling issues. There are many ways to generate risk estimates. Some researchers view all mathematical models as empirical (*3*), while others believe that biological or mechanistic realism can be captured within a mathematical equation. Are theoretical models superior to empirical models, or are there many ways to reasonably generate quantitative estimates of risk for radiation-induced mortality? This critical question was the organizing principle for the NASA workshop where the work described in this paper was presented.

DATA

Between 1970 and 1992, the JANUS program in the Biological and Medical Research Division at Argonne National Laboratory (ANL) compiled a database on the response of both sexes of an F$_1$ hybrid mouse, the B6CF$_1$ (C57BL/6 × BALB/c), to external whole-body irradiation by ^{60}Co γ rays and fission neutrons—20–40,000 animals (depending on level of pathology) distributed across 13 studies (*4*). Three basic patterns of exposure for both neutrons and γ rays were investigated: single exposures, 24 once-weekly exposures, and 60 equal once-weekly exposures. All irradiations were terminated at predetermined total doses, with dose calculated in centigrays at the midline

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of the mouse (*5*). The majority of the ANL studies were designed to study the biological consequences of occupational levels of exposure to radiation on young adult animals (100 days of age at the onset of exposure); limited data also exist for exposure of younger and older animals.

APPROACH

Neutron doses less than 1 Gy and γ-ray doses below 10 Gy were arbitrarily chosen to represent the lower-dose range in the JANUS data. Analyses were divided into two general categories, those dealing with control comparisons and those used to generate dose–response models. Kaplan-Meier analyses (*6*) were used to identify the lowest dose within a radiation quality and sex that produced a mortality experience that was significantly different from that observed for a concurrent control population. Dose–response analyses were performed to examine the shape of the response at lower doses, and to identify a dose within the upper region of the low-dose range where a shift in the shape of the dose response occurred. All analyses were repeated for a set of four combined pathology end points—all-cause mortality, and death caused by either solid-tissue tumor, tumor of connective tissue origin, or tumor of epithelial tissue origin.

All dose–response analyses were based on a proportional hazard model framework (*7*):

$$\lambda(t;z) = \lambda_0(t)\exp[fn(z)], \quad (1)$$

where $\exp[fn(z)]$ is the relative risk and z is a linear function of covariates that was parameterized in two different ways. The first parameterization, like analysis of variance in a linear model setting, used binary (0 or 1) indicator variables for each dose group used in the analysis. In other words, the model was set up so that the control group was always the baseline of comparison:

$$fn(z) = \sum \beta_i I_i, \quad (2)$$

where $I_i = 1$ if dose $= i$, 0 otherwise. In the second parameterization scheme, the model was set up like an analysis of covariance in a linear model setting:

$$fn(z) = \beta_1 I_1 + \beta_2 \text{ dose} + \beta_3 \text{ dose } I_1, \quad (3)$$

where dose (total accumulated dose) was treated as a continuous predictor variable and $I_1 = 1$ if dose was greater than a fixed value specified by the investigator, 0 otherwise. This parameterization allowed a single constant and/or an adjustment to the dose coefficient to be made to the basic dose–response model (β_2 dose) at higher levels of exposure.

PRELIMINARY RESULTS

Distributions of dose points that differed between patterns of exposure within radiation quality and even between sexes within patterns of exposure make it difficult to draw definitive conclusions. For the protracted exposures (60 once-weekly) most relevant to space flight, a significant mortality effect could be detected at a neutron dose of 14 cGy and a γ-ray dose as low as 3 Gy. A detectable mortality effect for a single dose of neutrons also occurred within the range of 10–20 cGy, but dropped to 86 cGy for a single exposure to γ rays. Although detectable mortality effects for the three pathology end points considered in these analyses usually occurred at the same dose, the highest risks were almost always associated with deaths from tumors of epithelial tissue origin. Although the doses associated with detectable mortality effects were similar for the two sexes whenever comparable exposure data were available, the risks for females were usually higher than those estimated for males at the same dose.

The dose–response model parameterization of Eq. (2) revealed distinctly nonlinear dose responses for all pathology end points associated with exposure to neutrons (up to 1 Gy). The response for deaths from tumors of epithelial tissue origin associated with single exposures to γ rays (up to 8 Gy) also exhibited significant nonlinearity, and the other pathology end points exhibited milder curvature. At least for solid-tissue tumors, the response of males and females was nearly identical for exposure to γ rays, but for neutron exposures, females had risks that were consistently higher than those observed for males. Protracting the dose of γ rays resulted in the same pattern of reduced risks (less than 2 at 6 Gy) that has been observed for life shortening (*8*). Up to a total body burden of 80 cGy, the neutron-induced risk estimates for total mortality caused by acute and 60 once-weekly exposures exhibited a quadratic-like response with no sign of a protraction effect—a response that is also consistent with previous observations on life shortening (*9*). Like the control contrasts performed at the lowest available doses, Eq. (3) was intended to detect changes (i.e. curvature) in the risk of mortality at doses judged to be at the higher end of the lower-dose range of the ANL data selected used for these analyses. Although instances of curvature consistent with those revealed empirically by Eq. (2) were detected, most of the responses for strata defined by radiation quality, exposure pattern, sex and pathology were described adequately by a relative risk term containing nothing more than a simple dose term representing the total dose received.

DISCUSSION

In this paper, we have reported results for only one of the three modeling tasks funded under the auspices of a NASA grant—the empirical modeling approach. Control contrasts at the lowest doses available within the ANL data revealed doses where no statistically significant mortality effect could be detected. Whether these represent real thresholds or are simply an artifact of inadequate statistical power is not known. Currently, these doses are being examined to determine whether the lack of detectable mortality is also accompanied by a lack of change in the fre-

quency of lesions that were observed at death but were judged not to have either caused or contributed to the death of the animal. The models using the ANOVA-like parameterization (Eq. 2) generated a summary statistic—the β term, or log relative risk—for each dose group used in the analyses. These summary values became the response variables for simple regression models used to describe their dose-related behavior. Although these regressions were performed to enable risk interpolations for nonobserved levels of dose, the approach is not too dissimilar from previous analyses of the JANUS data that used other synoptic measures of the life table (e.g. life shortening, mean after survival and cumulative risk) as response variables for regression analysis (*8, 10*). Equation (3), with its dose-dependent opportunities for a change in the dose response (i.e. ANCOVA-like indicator variables), was intended to provide a more numerically rigorous complement to the purely empirical regressions of Eq. (2). Even if they exist, common patterns of response are hard to detect when there are data gaps between the sexes, and when patterns of exposure differ in their available dose ranges and dose distributions. Nevertheless, a general consistency of data interpretation found for the different parameterizations of the Cox models reported in this paper repeat a previously reported convergence of interpretation that was demonstrated for Cox model and regression estimates of life shortening, RBE and DREF (*11*).

Our colleague Peter Groer from the University of Tennessee has been analyzing the same data used for our analyses with his own empirical models—fully parametric Bayesian models parameterized to estimate change points in the dose response (*12*). David Hoel and his colleagues at the Medical University of South Carolina are fitting a mechanistic two-stage model of carcinogenesis to these data. Although in progress, the data interpretations from these alternative modeling approaches have not been compared to our own. Clearly, the motivation and the numerical features of our empirical Cox models, the parametric Bayesian model, and the biologically motivated clonal expansion model differ dramatically. Every risk model imposes a structure on the data from which it was derived. Useful models match their imposed structure with the structure that is embedded within the data. In the spirit of a Bayesian prior probability, it is our belief that a convergence of data interpretation has more to do with the meticulousness of the modeling effort than it has to do with the specifics of the numerical methods or the modeling philosophy used to arrive at the interpretations. Time will tell whether the pragmatic quote that began this paper can be generalized to include risk models for radiation carcinogenesis: ''It does not matter whether the model is empirical or theoretical, it only matters if the model can predict radiation-induced health risks for crew members during space flight.''

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