RADIATION RESEARCH **119,** 39–56 (1989)

Dose–Response Modeling of Life Shortening in a Retrospective Analysis of the Combined Data from the JANUS Program at Argonne National Laboratory[1]

BRUCE A. CARNES, DOUGLAS GRAHN, AND JOHN F. THOMSON

Biological, Environmental, and Medical Research Division, Argonne National Laboratory, Argonne, Illinois 60439-4833

CARNES, B. A., GRAHN, D., AND THOMSON, J. F. Dose–Response Modeling of Life Shortening in a Retrospective Analysis of the Combined Data from the JANUS Program at Argonne National Laboratory. *Radiat. Res.* **119,** 39–56 (1989).

Life shortening was investigated in both sexes of the B6CF$_1$ (C57BL/6 × BALB/c) mouse exposed to fission neutrons and ^{60}Co γ rays. Three basic exposure patterns for both neutrons and γ rays were compared: single exposures, 24 equal once-weekly exposures, and 60 equal once-weekly exposures. Ten different dose–response models were fitted to the data for animals exposed to neutrons. The response variable used for all dose–response modeling was mean after-survival. A simple linear model adequately described the response to neutrons for females and males at doses ≤80 cGy. At higher neutron dose levels a linear–quadratic equation was required to describe the life-shortening response. An effect of exposure pattern was observed prior to the detection of curvature in the dose response for neutrons and emerged as a potentially significant factor at neutron doses in the range of 40–60 cGy. Augmentation of neutron injury with dose protraction was observed in both sexes and began at doses as low as 60 cGy. The life-shortening response for all animals exposed to γ rays (22–1918 cGy) was linear and inversely dependent upon the protraction period (1 day, 24 weeks, 60 weeks). Depending on the exposure pattern used for the γ-ray baseline, relative biological effectiveness (RBE) values ranged from 6 to 43. Augmentation, because it occurred only at higher levels of neutron exposure, had no influence on the estimation of RBE$_m$.

INTRODUCTION

Life shortening has been an important end point in the analysis of animal experiments involving external exposure to radiation because it summarizes, in a single index, the cumulative effect of all injuries experienced by an organism. This end point has been used to investigate concepts in radiation biology, as well as to provide a basis for setting safety standards for occupational levels of radiation exposure. Particular interest has focused on life-shortening estimates from mouse studies involving neu-

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0033-7587/89 $3.00

tron exposure because of the lack of available human data after the recent revision of dosimetry for the A-bomb survivors (*1, 2*).

Interest in occupational levels of neutron exposure has focused attention on the shape of the dose–response curve at low doses and on the effect of dose fractionation or protraction. Several studies (*3–7*) have suggested that the initial portion of the neutron dose response can be adequately described by a linear model. However, the dose level at which linearity ceases to be appropriate (ranging from 10 to 50 cGy) has differed depending on the dose rate and mouse strain investigated, and it has been reported (*4, 6, 7*) that the rate of life shortening increases with decreasing neutron dose. While the effectiveness of γ radiation decreases with dose fractionation or protraction, numerous studies (*4–6, 8–11*) have reported an increase in life shortening (an augmentation effect) with dose fractionation or protraction at high levels (greater than 40 cGy) of neutron exposure.

The dependency of the response to neutrons on the level and pattern of exposure has led several investigators (*5, 7*) to suggest that no single dose–response equation can adequately describe both the low-dose and high-dose neutron response. Any dose–response function (e.g., $Y = a + b \times d + c \times d^2$) applied to the entire dose range places inherent constraints on the form of the modeled response by the very nature of its mathematical form. For example, the linear–quadratic function (a parabola) above will reach a maximum at a dose of $-b/2c$ (assuming c to be negative), and any responses at dose levels beyond this maximum are likely to be underestimated. These constraints on the form or shape of the dose response not only will affect prediction but may also affect the slope coefficients used in the estimation of the relative biological effectiveness (RBE). If a linear–quadratic model is inappropriately fitted (i.e., a misspecified model) to a linear response (or vice versa), the ratio of linear slopes will result in a distorted estimate of the RBE value. Even if a particular function is correctly specified for the entire dose range for neutrons, the resulting slope coefficient used to generate an RBE value may not accurately reflect the estimate of this value in an analysis restricted to lower doses.

Resolution of the above issues concerning neutron dose response requires an extensive data base. Over the last 25 years, the JANUS program (*12*) in the Biological, Environmental, and Medical Research Division at the Argonne National Laboratory (ANL) has compiled such a data base on the response of both sexes of an F_1 hybrid mouse exposed to external whole-body irradiation by ^{60}Co γ rays and fission neutrons for several different patterns of exposure. The purposes of this paper are to: (i) investigate the form of the dose response for the neutron exposures at low doses and identify the dose range for which a linear response may be adequate; (ii) test the effect of exposure pattern on the dose–response relationship; (iii) investigate alternatives to the linear–quadratic model that may accommodate a neutron dose range encompassing higher doses; and (iv) provide a set of neutron RBE values for life shortening from the ANL data base. These are not new issues; Thomson *et al.* (*3, 7–9, 13–16*) have addressed most of these questions in their series of papers on life shortening. However, now that all of the JANUS experiments have in this series been completed, it is appropriate to consider all of the experiments simultaneously rather than individually. It will become evident to the reader that unfortunate gaps in the data base will adversely affect our ability to address definitively some of the questions posed in this paper, but these limitations are inherent in any retrospective study.

MATERIALS AND METHODS

Animals and Irradiation Procedures

All analyses presented in this paper employed both sexes of the $B6CF_1$ (C57BL/6 × BALB/c) mouse, which has been used at ANL for 35 years. Details concerning the radiation sources, animal care, facilities, experimental design, irradiation procedures, and the basic objectives of the JANUS research program have been previously described (*8, 12*). Fission neutron (mean energy approx 0.85 MeV with 2–3% γ-ray contamination) irradiations were performed at ANL with the JANUS biomedical research reactor. Gamma irradiations were performed in the division's high-level ^{60}Co γ-irradiation facility. All mice were irradiated at approximately 110 days of age; control mice were sham irradiated. Death checks were made daily. Dates of birth, irradiation, and death along with radiation exposure, animal number, and cage and experiment identification were stored in computer files for subsequent analysis.

Exposure Patterns

Three basic exposure patterns for both neutrons and γ rays are compared in the present analysis: single exposures, 24 equal once-weekly exposures, and 60 equal once-weekly exposures. The data for males exposed to γ rays also include two additional fractionated exposures, 22-h exposures for 5 days/week for either 23 or 59 weeks. These elapsed times are equal to those in the 24 and 60 once-weekly series. The duration of single exposures was approximately 20 min, and most weekly exposures were for 45 min per fraction. All irradiations were terminated at predetermined total doses with dose given in centigray to the midline of the mouse as determined by phantom dosimetry (*17*).

Statistical Methods

The response variable used for all dose–response modeling was mean aftersurvival (MAS). The MAS data [computed by the method of Hoel and Walburg (*18*)] used in the current analyses (Tables I and II) have been analyzed by exposure pattern and previously reported in a series of papers by Thomson *et al.* (*3, 7–9, 13–16*). When linear or linear–quadratic models were employed (see Table III), the linear slope coefficient (with sign reversed) was interpreted as the life-shortening coefficient.

All dose–response models employed were generated by weighted regression (*19*) using dose or functions of dose as predictor variables and the inverse variance of MAS as a weighting device. Coefficients for nonlinear models were estimated by iteratively reweighted least squares (IRLS) using PROC NLIN in SAS (Statistical Analysis System (*20*)). Initially, the models were fitted separately to each radiation quality, pattern of exposure, and sex to obtain parameter estimates and their standard errors. The regression models were then generalized to analysis of covariance (ANCOVA) by the use of binary indicator variables (*21*) representing group membership. The ANCOVA approach is a simple way of simultaneously generating regression estimates for subsets of the data (e.g., sex, exposure pattern) that are identical to those generated when the subsets are analyzed individually. In addition, interaction terms involving indicator variables from the ANCOVA model can be used to test whether heterogeneity for model parameters (e.g., slope, power) exists among the subsets (e.g., sex, exposure pattern) defined by the indicator variables.

A variety of dose–response models (Table III) were fitted to the neutron data. The linear (model 2), linear–quadratic (model 1), and Thomson (model 6) equations were used because they have been previously applied (*3, 7–9, 13–16*) to these data. Model 3 was included to represent a response based on the proportional reduction of mean aftersurvival (PRM). This model is equivalent to dividing the MAS response at each dose by the concurrent control and fitting the resulting PRM response to a linear equation constrained through an intercept of unity (or 100% if percentages are used). The model 3 parameterization avoids the absence of independence and the resulting complication of defining the covariance structure that is created by the PRM endpoint. Models 4 and 5 were included because Storer and Mitchell (*4*), in their analysis of data from ANL and Oak Ridge National Laboratory, employed these power function equations. Model 4 was applied to single exposures, and model 5 was applied to fractionated exposures.

These six models were fitted to the neutron data at a series of progressively increasing dose ranges (i.e., a control and any doses up to and including 10, 13.5, 21, 40, 60, 80, 120, 160, and 240 cGy) to investigate the form of the dose response at low doses, the effect of dose range on parameter estimation, and the effect of exposure pattern on the parameters of these models. Because available responses at neutron doses above the specified range were ignored, the resulting nine sets of data will be subsequently called the "truncated"

TABLE I

Mean Aftersurvival (MAS) with Standard Errors (SE) for Females and Males Given Single (1), 24 Once-Weekly (24), and 60 Once-Weekly Exposures (60) to Neutrons

			Females		*Males*	
Exposure	*Dose*	*Expt*	*MAS*	*SE*	*MAS*	*SE*
1	0	A	835.8	6.7	848.4	6.6
	0	B	850.6	7.5	878.3	13.5
	0	C	890.6	13.5	934.6	12.9
	1	D	856.2	7.2	—	—
	2.5	D	847.9	9.0	—	—
	5	C	850.6	11.5	—	—
	5	D	823.8	10.8	—	—
	10	C	826.7	12.8	875.8	13.7
	10	D	804.9	13.0	—	—
	20	A	759.1	9.8	789.1	9.9
	20	B	776.0	12.8	827.3	13.2
	20	D	797.4	13.3	—	—
	40	B	—	—	798.0	14.4
	40	D	753.0	15.5	—	—
	60	B	—	—	779.2	14.3
	80	A	667.3	13.5	723.9	14.1
	120	B	—	—	719.1	17.6
	160	B	645.7	17.0	713.6	18.1
	240	A	580.0	13.8	632.3	14.6
24	0	E	835.3	6.7	848.4	6.6
	0	F	889.7	16.3	927.8	13.9
	0	G	853.9	10.9	—	—
	0	H	864.9	13.3	—	—
	10	H	846.3	14.9	—	—
	20	F	799.4	7.8	845.4	8.0
	40	F	—	—	799.1	9.9
	60	F	—	—	762.3	14.7
	80	E	674.5	12.9	665.5	14.9
	80	G	694.4	10.6	—	—
	120	F	—	—	665.7	16.2
	160	F	595.9	13.1	630.7	15.2
	240	E	497.2	8.9	532.0	10.1
	240	G	551.8	9.6	—	—
60	0	L	851.6	7.7	898.9	9.2
	0	M	877.0	7.7	885.7	7.7
	2	M	870.7	8.1	894.6	8.0
	7.5	M	838.5	12.4	870.5	11.4
	13.5	M	809.4	11.2	855.2	11.3
	21	M	790.0	11.8	816.5	11.5
	30	M	771.0	15.3	778.6	16.3
	40	L	763.4	37.7	788.0	15.1
	40	M	717.4	18.8	804.7	17.6
	160	L	599.1	10.8	632.2	11.6

TABLE II

Mean Aftersurvival (MAS) with Standard Errors (SE) for Females and Males Given Single (1), 23-5 Days/Week (23), 24 Once-Weekly (24), 59-5 Days/Week (59), and 60 Once-Weekly (60) Exposures to γ Rays

			Females		*Males*	
Exposure	*Dose*	*Expt*	*MAS*	*SE*	*MAS*	*SE*
1	0	A	835.8	6.7	848.4	6.6
	0	B	850.6	7.5	878.3	13.5
	0	D	856.2	7.2	—	—
	22.5	D	844.4	8.6	—	—
	45	D	850.1	10.8	—	—
	90	A	790.4	8.9	810.2	9.7
	90	B	825.3	13.3	857.3	14.2
	90	D	822.4	14.0	—	—
	143	B	—	—	826.9	16.4
	206	B	—	—	806.5	15.1
	268	A	706.3	12.0	727.0	13.3
	417	B	706.5	26.5	743.5	17.5
	569	B	644.7	25.0	645.9	20.2
	788	A	481.8	14.8	501.6	15.8
23	0	P	—	—	857.3	14.6
	206	P	—	—	829.7	13.2
	417	P	—	—	805.6	21.8
	959	P	—	—	675.3	22.8
	1918	P	—	—	578.6	31.6
24	0	E	835.3	6.7	848.4	6.6
	0	F	889.7	16.3	927.8	13.9
	0	G	853.9	10.9	—	—
	206	F	—	8.8	802.1	7.7
	417	F	782.6	8.8	802.1	9.5
	807	G	704.8	9.3	—	—
	855	E	679.8	10.7	693.7	9.8
	959	F	610.1	11.2	723.9	12.1
	1110	E	—	—	618.9	14.0
	1918	F	—	—	441.0	12.5
	2690	G	350.5	6.7	—	—
59	0	Q	—	—	802.9	15.8
	528	Q	—	—	767.7	14.8
	1070	Q	—	—	718.7	15.8
	2460	Q	—	—	616.2	20.5
60	0	L	851.6	7.7	898.9	9.2
	0	M	877.0	7.7	885.7	7.7
	100	M	846.8	7.7	861.5	7.5
	200	M	819.5	14.8	840.9	14.2
	300	M	785.0	20.1	835.0	20.4
	417	L	785.7	40.9	862.4	16.0
	450	M	787.3	17.8	815.9	18.8
	600	M	747.6	19.1	798.5	19.4
	1918	L	620.9	10.4	625.0	11.4

TABLE III

Dose–Response Models Fitted to the Data for Neutron and γ-Ray Exposure

Model	*Equation*	*Description*
1	$\beta_0 + \beta_1 d + \beta_2 d^2$	Linear–quadratic
2	$\beta_0 + \beta_1 d$	Linear
3	$\beta_0(1 - \beta_1 d)$	Proportional reduction in MAS
4	$\beta_0 - \beta_1 d^{\lambda}$	Power function
5	$\beta_0 - \beta_1 d^{\lambda} n^{1-\lambda}$	Power function
6	$(1/\beta_0 + \beta_1 d^{\lambda})^{-1}$	Thompson
7	$\theta_1 + \theta_2 d \exp(-\theta_4 d) + \theta_3 d^2$	Dampening factor
8	$\theta_1 + \theta_2 d + \theta_3 d^2 \exp(-\theta_4 d)$	Dampening factor
9	$\theta_1 + (\theta_2 d + \theta_3 d^2) \exp(-\theta_4 d)$	Dampening factor
10	$\Phi_1 + \Phi_2 d + \Phi_3 (\Phi_4 - d)^2 I$	Polynomial spline[a]

[a] I is an indicator variable that is equal to 1 if $d \geq \phi_4$ and zero otherwise.

data. Within a truncated data set, only those exposure patterns that could be represented by at least three dose points were included in the analysis. Within a pattern of exposure for any given analysis, only those experiments that had dose points less than or equal to the truncation point were included. When any given exposure pattern was represented by more than one experiment, a variance-weighted mean and standard error of the controls for the included experiments were calculated to represent the concurrent control for that exposure pattern. All of the dose–response models were also fitted to the γ-ray data, but for these data the entire dose range for each pattern of exposure was included in the analysis.

The effect of exposure pattern on the coefficients of a dose–response model for each radiation quality was tested by using ANCOVA. In all dose–response models, each exposure pattern was allowed to have a unique intercept. Then, depending on which model was being fitted, each exposure pattern was allowed to have its own linear, dose-squared (quadratic), and/or power coefficient. The significance of interaction terms in the ANCOVA model involving these parameters and indicator variables representing membership in an exposure pattern group were used to test for differences among patterns of exposure. Using the significance of the interaction terms as a test is formally identical to ignoring exposure pattern, fitting a single model to the pooled data, and testing for the increase in the error sums of squares (SSE) for this model relative to the SSE for a model where these parameters are allowed to vary by exposure pattern. Results for the latter approach, estimating common parameters for all terms except the intercept, are presented for all analyses. In order to evaluate the potential distortion of model parameters not associated with the intercept when the control for each exposure pattern is represented by a single variance-weighted mean, all dose–response analyses were repeated with intercepts within exposure patterns allowed to vary by experiment and dose-related parameters allowed, as usual, to vary by exposure pattern. Analyses were also performed with the model equations representing an exposure pattern constrained through the observed control values.

The power function equations (models 4 and 5), the Thomson equation (model 6), and the linear–quadratic equation (model 1) predict curvature regardless of the dose range employed. The linear model, a special case of models 4 or 5 with a power equal to unity, is also a special case of the linear–quadratic equation with a dose-squared coefficient equal to zero. Therefore, departure of the power parameter from unity or the significance of the coefficient for the dose-squared term was used to identify the neutron dose level at which curvature in the dose response could be first detected.

Alternatives to the standard linear and linear–quadratic equations applied to the entire dose range for neutron exposure were also explored. The first alternative employed an exponential dampening factor, identical with that used for cell-killing models (*22*), applied to either the linear term (model 7), the quadratic term (model 8), or both terms (model 9) in a linear–quadratic equation. Although a quadratic or a two-parameter linear–quadratic function could have been used, we put a simple linear function of dose in the exponential dampening factor [$\exp(-\theta_4 \times \text{dose})$]. The coefficients of these nonlinear models were estimated

by IRLS using PROC NLIN in SAS (*20*). Of these three models, the one that resulted in the smallest SSE for each pattern of exposure and sex was identified. This model was then generated for the entire (pooled) data set, ignoring pattern of exposure. The sum of the SSE values for the individual exposure patterns and the sum of the error degrees of freedom were then compared to the SSE for the pooled model to test the null hypothesis of no exposure pattern effect. Finally, the dampening-factor models (pattern specific and pooled) were compared to the equivalent linear–quadratic model to determine whether the addition of the dampening terms significantly reduced the SSE. A nonsignificant reduction in the SSE was interpreted to mean that the dampening-factor model provided no better fit to the dose–response than the linear–quadratic model.

The second alternative to a standard linear–quadratic model investigated was a polynomial spline model (*23*) applied to the entire dose range available for neutrons. In this approach, the lower dose range was fitted by a linear equation, and the higher dose range was simultaneously fitted by a linear–quadratic equation. The unknown dose value at which these two equations were joined was determined by including a join point parameter in the spline model to be estimated like any other coefficient. Again, parameter estimation was accomplished by IRLS using PROC NLIN in SAS (*20*). The pattern of hypothesis testing in the analysis of spline models was identical with that used for the dampening-factor models, with the reduction in SSE used as a test criterion for determining whether the dose response for exposure patterns differed and whether the more complex polynomial spline model was superior to the standard linear–quadratic equation when applied to all the available data for exposure to neutrons.

RESULTS

Initial analyses indicated a consistently larger life-shortening coefficient for females as compared to males. Therefore, subsequent results will be based on analyses conducted separately for each sex. Parameter estimates for the PRM model (model 3), which is a reparameterized version of the linear model with the life-shortening coefficient estimated as the product of the intercept and the slope term, will not be presented. Similarly, the results for the model 5 form of the power function equation will not be presented because it is just a reparameterized version of model 4. Reparameterization has no effect on RBE estimation. Parameter estimates for dose–response models using a single variance-weighted mean for the control of an exposure pattern were nearly identical to those generated from models allowing for experiment-specific intercepts or constrained through the experiment-specific control values. Therefore, only the analyses employing the variance-weighted control values will be presented.

Truncated Neutron Data

Results of the analyses for models 1 (linear–quadratic) and 2 (linear) applied to the truncated data for neutron exposure are presented in Tables IV (females) and V (males). Curvature (i.e., a significant dose-squared coefficient) in the dose response for either sex could not be detected until the 160-cGy dose point was included in the dose range modeled. The life-shortening term in the analyses of the data for females was significant ($P < 0.01$) when the maximum dose was only 10 cGy. In the analyses of the data for males, the life-shortening term was not statistically significant ($P = 0.01$) until the 21-cGy point was included in the dose range modeled. The coefficient for the dose-squared term in model 1 for the 24 once-weekly data never attained significance for males and only became significant ($P = 0.03$) when the 240-cGy dose point was included in the analyses of the data for females. As larger neutron doses

TABLE IV

Days Lost per Centigray (β_1), Quadratic Coefficient (β_2), Their Standard Errors (SE), the Model Degrees of Freedom (*df*), and Error Sums of Squares (SSE) for Models 1 and 2 and the Pooled Model (P) Fitted to the Truncated Data for Females Given Single (1), 24 Once-Weekly (24), and 60 Once-Weekly Exposure (60) to Neutrons

Max dose	*Exposure*	β_1	*SE*	β_2	*SE*	*SSE*	*df*	*Expt*[a]	*Cont*[b]	*SE*
10	1	5.73	0.84	—	—	1.2	3	D	856.2	7.2
	60	5.14	0.74	—	—	0.2	1	M	877.0	7.7
	P	5.54	0.58	—	—	1.4	5	—	—	—
13.5	1	5.73	0.84	—	—	1.2	3	D	856.2	7.2
	60	5.13	0.25	—	—	0.2	2	M	877.0	7.7
	P	5.32	0.38	—	—	1.4	6	—	—	—
21	1	3.51	0.74	—	—	4.7	4	D	856.2	7.2
	24	3.87	0.41	—	—	0.3	1	FH	874.8	10.3
	60	4.44	0.34	—	—	1.0	3	M	877.0	7.7
	P	4.00	0.32	—	—	7.2	10	—	—	—
40	1	2.77	0.42	—	—	6.4	5	D	856.2	7.2
	24	3.87	0.41	—	—	0.3	1	FH	874.8	10.3
	60	3.94	0.26	—	—	2.7	5	M	877.0	7.7
	P	3.43	0.26	—	—	14.9	13	—	—	—
80	1	2.43	0.30	—	—	23.9	7	AD	845.3	4.9
	24	2.04	0.14	—	—	4.0	3	EFGH	848.5	5.0
	60	3.94	0.26	—	—	2.7	5	M	877.0	7.7
	P	2.30	0.17	—	—	57.3	17	—	—	—
160	1	3.50	0.37	−0.014	0.003	15.7	8	ABD	846.9	4.1
	24	2.49	0.25	−0.006	0.002	3.6	3	EFGH	848.5	5.0
	60	3.99	0.33	−0.014	0.002	4.3	6	LM	864.3	5.4
	P	3.05	0.24	−0.009	0.001	47.0	21	—	—	—
240	1	2.69	0.37	−0.007	0.002	34.5	9	ABD	846.9	4.1
	24	2.28	0.32	−0.004	0.001	22.4	5	EFGH	848.5	5.0
	60	3.99	0.33	−0.014	0.002	4.3	6	LM	864.3	5.4
	P	2.46	0.21	−0.005	0.001	102.7	24	—	—	—

[a] Experiment codes from Table I used in the analysis.
[b] Variance-weighted mean used as the control response.

were included in the truncated data for either sex, the dose-squared term became smaller in magnitude but had greater statistical significance.

Statistical significance for the effect (i.e., slope heterogeneity) of exposure pattern was attained ($P = 0.01$) in the analysis of the data for females when the truncated data set included the 80-cGy dose point. There was a suggestion ($P = 0.08$) of slope heterogeneity among the three exposure patterns when the maximum dose in the truncated data was 40 cGy. A one-tailed *t* test of slope equality between females given a maximum dose of 40 cGy in a single exposure and females receiving the same maximum dose in 60 once-weekly exposures was significant ($P = 0.02$). In the analysis of the data for males, slope heterogeneity was suggested ($P = 0.11$) when the trun-

TABLE V

Days Lost per Centigray (β_1), Quadratic Coefficient (β_2), Their Standard Errors (SE), the Model Degrees of Freedom (*df*), and Error Sums of Squares (SSE) for Models 1 and 2 and the Pooled Model (P) Fitted to the Truncated Data for Males Given Single (1), 24 Once-Weekly (24), and 60 Once-Weekly Exposure (60) to Neutrons

Max dose	*Exposure*	β_1	*SE*	β_2	*SE*	*SSE*	*df*	*Expt*[a]	*Cont*[b]	*SE*
21	60	3.36	0.55	—	—	2.73	3	M	885.7	7.7
30	60	3.60	0.40	—	—	3.18	4	M	885.7	7.7
40	S	2.02	0.32	—	—	.43	1	B	878.3	13.5
	24	3.06	0.64	—	—	2.38	1	F	927.8	13.9
	60	2.95	0.46	—	—	8.66	5	M	885.7	7.7
	P	2.77	0.30	—	—	14.53	9	—	—	—
60	S	1.64	0.26	—	—	1.42	2	B	878.3	13.5
	24	2.65	0.44	—	—	4.37	2	F	927.8	13.9
	60	2.95	0.46	—	—	8.66	5	M	885.7	7.7
	P	2.38	0.27	—	—	23.60	11	—	—	—
80	S	1.49	0.29	—	—	12.81	4	AB	854.2	5.9
	24	2.10	0.36	—	—	15.12	3	EF	863.0	6.0
	60	2.95	0.46	—	—	8.66	5	M	885.7	7.7
	P	1.90	0.21	—	—	53.69	14	—	—	—
120	S	1.28	0.22	—	—	16.99	5	AB	854.2	5.9
	24	1.88	0.26	—	—	19.11	4	EF	863.0	6.0
	60	2.95	0.46	—	—	8.66	5	M	885.7	7.7
	P	1.66	0.17	—	—	72.17	16	—	—	—
160	S	1.97	0.41	−0.007	0.003	12.08	5	AB	854.2	5.9
	24	2.22	0.59	−0.004	0.004	2.55	4	EF	863.0	6.0
	60	3.26	0.39	−0.010	0.002	7.49	6	LM	891.1	5.9
	P	2.23	0.35	−0.005	0.002	90.61	19	—	—	—
240	S	1.46	0.32	−0.002	0.001	18.83	6	AB	854.2	5.9
	24	2.05	0.36	−0.003	0.001	22.36	5	EF	863.0	6.0
	60	3.26	0.39	−0.010	0.002	7.49	6	LM	891.1	5.9
	P	1.96	0.26	−0.003	0.001	126.63	21	—	—	—

[a] Experiment codes from Table I used in the analysis.
[b] Variance-weighted mean and standard error (SE) used as the control response.

cated data included the 60-cGy dose point, but statistical significance ($P = 0.04$) for this effect was not fully attained until the 120-cGy data point was included in the analysis. The minimum dose at which an effect of exposure pattern in the data for males could be detected ($P = 0.02$) was reduced to 60 cGy and was suggestive ($P = 0.08$) at 40 cGy when the 24 once-weekly data, which have only limited information at low doses, were deleted. Once curvature in the dose response for either sex was detected, exposure pattern influenced both the linear and the dose-squared coefficient of the linear–quadratic equation. The effect of exposure pattern was observed prior to the detection of curvature in the dose response and emerged as a potentially significant factor at neutron doses in the range of 40–60 cGy.

Beginning with a maximum dose of 21 cGy in females (Table IV) and 40 cGy in males (Table V), another pattern associated with mode of exposure was evident. In all analyses of truncated data beyond these dose values, the life-shortening coefficient (linear term) for animals given single exposures was significantly less than the life-shortening term for animals given 60 once-weekly exposures. This consistent increase in the magnitude of the life-shortening coefficient with dose protraction included the response to 24 once-weekly exposures in the analyses of the truncated data for males. In females, the response of mice receiving 24 once-weekly exposures was erratic, but this may have resulted from the limited low- and medium-dose information available for this exposure pattern (Table I). With the exception of the one exposure pattern in females, there appears to be an augmentation of life shortening for protracted exposure to neutrons that becomes significant at doses as low as 60 cGy.

Power Models

Prior to the statistical detection of curvature (i.e., 160 cGy) in the dose response, another pattern in the analyses of the truncated data for either sex was apparent. The life-shortening coefficient (exposure pattern specific or the pooled estimate) increased as the maximum dose in the truncated data set was decreased (see Tables IV and V). This trend in the life-shortening coefficients suggests that while the linearity imposed by model 2 could not be rejected when compared to the curvature imposed by the linear–quadratic equation, there may be curvature in the low-dose range that could be described by alternative nonlinear models. Therefore, a complete set of analyses on the truncated neutron data and the full array of γ-ray data for each sex was performed by using the power function equation (model 4) and the Thomson equation (model 6). Initial analyses suggested that while the Thomson model does not resemble the power function algebraically, it provided nearly identical estimates of the power parameter, employed the same number of degrees of freedom, explained approximately the same amount of variation in the dose response, and when also applied to the γ-ray data generated very similar estimates of the RBE value. Exactly the same data that were used for the evaluation of models 1 and 2 were used in the analyses of the alternative nonlinear models.

A test for the significance of the reduction in the SSE achieved by fitting each exposure pattern with its own unique power function versus ignoring pattern of exposure and fitting a single model to the pooled data from all exposure groups demonstrated that a single model was appropriate for every data set analyzed except the truncated data set that included the 240-cGy point in the analyses of data for males ($P = 0.003$). Nevertheless, when the power function equations for individual patterns of exposure were examined, the power parameter (λ) did not differ from unity in any analysis for either sex until the 160-cGy point was included in the truncated data set. When the power parameter in model 4 is equal to unity, the equation for the power function reduces to the simple linear model that adequately described the dose response for this dose range in the analyses described for the truncated neutron data. All tests comparing the reduction in SSE for each exposure pattern and sex by the power function relative to a simple linear model when the maximum dose was below 160 cGy were nonsignificant. At 160 cGy and beyond, the estimates for the power param-

TABLE VI

Days Lost per Centigray (β_1) Estimates for Both Sexes and Each Exposure Pattern Generated from Linear Models Fitted to the Entire Dose Range for Exposure to γ Rays

Sex	*Weeks of exposure*	*Exposures per week*	β_1	*SE*	*SSE*[a]	*df*	*Expt*	*Cont*[b]	*SE*
F	1	1	0.45	0.03	22.6	8	ABD	846.9	4.1
	24	1	0.20	0.02	9.2	3	EFG	845.8	5.4
	60	1	0.13	0.01	9.6	6	LM	864.3	5.4
M	1	1	0.41	0.04	33.7	7	AB	854.2	5.9
	24	1	0.22	0.02	39.4	5	EF	863.0	6.0
	23	5	0.16	0.02	2.9	3	P	857.3	14.6
	60	1	0.14	0.01	9.2	6	LM	891.1	5.9
	59	5	0.08	0.003	0.1	2	Q	802.9	15.8

[a] Sums of squares error for the model and the corresponding degrees of freedom (*df*).
[b] Variance-weighted mean and standard error (SE) used as the control response.

eter in model 4 fitted to the truncated neutron data were significantly less than unity ($P = 0.05$) for either sex. However, when larger neutron doses were included in the analysis, it was apparent that the SSE for the power function equation and the linear–quadratic model were comparable for all patterns of exposure and both sexes. In summary, a simple linear model at low doses or a linear–quadratic model at high doses appears to adequately describe the dose response for exposure to neutrons for all patterns of exposure considered in this study.

Gamma Rays

The γ-ray data included the same exposure patterns as the neutron data with the addition of two fractionated-exposure groups (22-h exposures for 5 days/week for 23 and 59 elapsed weeks) for the males (Table II). All available dose information for each pattern of exposure was used for the investigation of dose–response relationships in the γ-ray data; that is, no analyses of truncated data were performed. A single variance-weighted mean and the standard error for MAS were again used to represent the control for an exposure pattern. Results of the dose–response analyses for both sexes are summarized in Table VI.

A simple linear equation (model 2) fitted separately to each pattern of exposure and either sex accounted for a minimum of 94% of the variation in the dose response of MAS. The estimated intercepts for the linear models were, with the exception of the 24 once-weekly exposure pattern for males, randomly distributed within one standard error of the observed control mean representing an exposure pattern. Preliminary analyses, allowing for experiment-specific intercepts rather than a single estimate for each exposure pattern, had the same relationships between observed and estimated intercepts, explained similar amounts of variation, and generated nearly identical slope estimates as those presented in Table VI. When contrasted with a linear–quadratic equation (model 1), a simple linear function of dose (model 2) was

TABLE VII

Linear (θ_2), Quadratic (θ_3), and Dampening (θ_4) Coefficients for Model 7 Applied to the Entire Dose Range for Exposure to Neutrons for Each Pattern of Exposure and Sex

Exposure										
Sex	*Pattern*	θ_2	*SE*	θ_3	*SE*	θ_4	*SE*	*SSE*[a]	*df*	*L/Q*[b]
F	1	−4.51	0.67	−0.003	0.001	0.011	0.002	13.7	8	34.5
	24	−2.68	1.02	−0.002	0.004	0.005	0.006	21.2	4	22.4
	60	−3.99	0.33	0.014	0.002	—	—	4.3	6	4.3
	P	−3.75	0.51	−0.003	0.001	0.008	0.002	73.4	23	102.7
M	1	−2.62	0.90	−0.003	0.001	0.011	0.005	12.3	5	18.8
	24	−2.07	0.81	0.005	0.031	−0.001	0.010	22.4	4	22.4
	60	−4.31	1.42	−0.007	0.004	0.014	0.011	6.5	5	7.5
	P	−2.44	0.63	−0.002	0.002	0.005	0.004	121.6	20	126.6

[a] Sums of squares error for the model and the corresponding degrees of freedom (*df*).
[b] SSE for the linear–quadratic equations fitted to the entire dose range.

found to adequately describe the dose–response relationship. In addition, the estimated value for the power parameter did not significantly differ from unity when power functions were fitted to each exposure pattern; this also indicates linearity of the dose–response in the γ-ray data. It should also be noted that when linear equations were fitted to the exposure patterns simultaneously by ANCOVA, 97% of the variability in MAS was explained by the ANCOVA model with a minimum of 17 degrees of freedom (in females) available for estimating the error term; this suggests that adequacy of the linear fit was not simply a product of fitting saturated models to each exposure pattern. The lack of systematic bias in the predicted control values provided additional evidence for linearity in the gamma-ray data for these experiments. However, for the two sexes, each pattern of exposure required a unique linear dose–response equation ($P < 0.001$). As dose protraction or dose fractionation was increased (Table VI), the days lost per centigray decreased and this trend was consistent for both sexes.

Dampening-Factor Models

The three models with a dampening factor (models 7, 8, and 9; Table III) were applied to the entire dose range for exposure to neutrons for each pattern of exposure and sex. As in previous analyses, a single variance-weighted mean and standard error were used to represent the control value for each pattern of exposure. The three models accounted for a similar amount of variation in the MAS response for either sex and all exposure patterns except the single exposure group. In the analyses of either sex given a single exposure to neutrons, a dampening factor applied to the linear term of a linear–quadratic equation (model 7) provided an improved fit relative to the other two models. Therefore, model 7 was selected as the representative of this class of models and the results of fitting this equation to the data for neutron exposure are summarized in Table VII.

The SSE resulting from the linear–quadratic equation fitted to these data and described earlier is repeated in Table VII for purposes of comparing the relative goodness-of-fit provided by these models. When the dampening factor in model 7 is equal to zero, this model reduces to an ordinary linear–quadratic equation. A test of the reduction in the SSE associated with fitting model 7 to each exposure pattern relative to a single model for all exposure patterns was significant for females ($P = 0.03$) and males ($P = 0.01$); hence a dampening-factor model that ignores pattern of exposure is inappropriate. However, the coefficient for the dampening factor did not significantly differ from zero for any exposure pattern except for females ($P < 0.05$) receiving a single exposure of neutrons. The dose response for all other exposure patterns was adequately described by a linear–quadratic equation. If the linear term for model 7 (column labeled θ_2 in Table VII) is interpreted as an estimate of days lost per centigray, the life-shortening estimates for the dampening-factor model are generally comparable to those reported at lower maximum doses in the analyses of the truncated data.

Polynomial Spline Model

A spline model (model 10), with an initial linear equation and a terminal linear–quadratic equation, was also fitted to the entire dose range for neutron exposure for each sex and exposure pattern. The dose value (join point) where the two equations must meet (i.e., give the same predicted response) was negative, less than the lowest observed dose, or small (less than 6 cGy) for all analyses except the response by males to 24 once-weekly exposures to neutrons, where the join point was estimated to be large and positive (276 cGy). The latter result agrees with the earlier finding that the dose-squared term in model 1 never attained statistical significance in any of the analyses of truncated data for males receiving 24 once-weekly exposures to neutrons. An extreme estimate (small or large) for the join point suggests that a single equation (linear for males receiving 24 once-weekly exposures and a linear–quadratic model for all others) adequately described the dose response for all exposure patterns for either sex. Consequently, the additional parameter (the join point) in the polynomial spline did not reduce the SSE sufficiently to warrant its inclusion in the model for these data.

RBE Values

RBE values obtained from the ratio of linear coefficients for the two radiation qualities are summarized in Table VIII. For neutrons, the coefficients were derived from the linear models fitted to those truncated data sets for which an effect of exposure pattern had not yet emerged (i.e., we used a common linear response to neutrons at low doses for all patterns of exposure). For the γ-ray data, the coefficients were obtained from the linear models fitted to the entire data set for each pattern of exposure (single, fractionated, and continuous). RBE values calculated from power functions are not presented because the estimated power coefficient in the range of doses presented for neutron exposure in Table VIII did not differ from unity; thus the power function equation reduces to the linear equation already being used to represent the dose response.

TABLE VIII

Matrix of RBE Values and (Standard Errors) for Both Sexes Calculated from the Ratio of Dose Coefficients Generated from Linear Dose–Response Models

	γ Rays		Neutrons			
			Maximum dose in truncated data			
Sex	Weeks of exposure	Exposures per week	10	13.5	21	40
F	1	1	12.3 (1.5)	11.8 (1.2)	8.9 (0.9)	7.6 (0.8)
	24	1	27.7 (4.0)	26.6 (3.3)	20.0 (2.6)	12.9 (2.1)
	60	1	42.6 (5.5)	40.9 (4.3)	30.8 (3.4)	26.4 (2.8)
			21	30	40	60
M	1	1	8.2 (1.6)	8.8 (1.3)	6.8 (1.0)	5.8 (0.9)
	24	1	15.3 (2.9)	16.4 (2.3)	12.6 (1.8)	10.8 (1.6)
	23	5	21.0 (4.3)	22.5 (3.8)	17.3 (2.9)	14.9 (2.5)
	60	1	24.0 (4.3)	25.7 (3.4)	19.8 (2.6)	17.0 (2.3)
	59	5	42.0 (7.1)	45.0 (5.3)	34.6 (4.0)	29.8 (3.6)

RBE values ranged from 8 to 43 for females and from 6 to 42 for males. The augmentation effect associated with protraction of neutron exposure had no influence on these RBE values because they were, as stated, based on truncated data for neutrons obtained prior to the emergence of this effect. The range of RBE values for any given row (reflecting the effect of dose range for neutron exposure) in Table VIII is much less than the range of RBE values in any given column; therefore, the decreasing effectiveness of γ rays with dose protraction was primarily responsible for the range of RBE values presented.

DISCUSSION

The conclusions derived from these analyses using a combined data base from the JANUS experiments are in basic agreement with those previously reported by Thomson *et al.* (*3, 7–9, 13–16*) and Storer and colleagues (*4–6*). A linear model adequately described the neutron response below 160 cGy for either sex. However, if there had been more dose information between 80 and 160 cGy, the range of observed linearity might have been reduced. In both sexes, there was a significant inverse relationship between the maximum neutron dose considered and the rate of life shortening per centigray within the dose range for which the hypothesis of linearity could not be rejected. This increased life shortening with decreasing dose suggests

nonlinearity, but neither the curvature imposed by a linear–quadratic equation nor the nonlinear models of Thomson (model 6) or Storer (model 4 or 5) could provide a better fit than that afforded by a simple linear equation.

As was previously reported (*4–6, 9–11*), augmentation of life shortening with dose protraction was seen only after exposure to relatively high doses of neutrons (80 cGy). If the data for 24 once-weekly exposures to neutrons are not considered, augmentation of life shortening was observed at 40 cGy in females and 60 cGy in males. In these analyses, the augmentation effect was observed in both sexes but was most pronounced in males. In the analyses of the data for males, augmentation was apparent even with the inclusion of data for the 24 once-weekly exposure pattern. The life-shortening response for either sex exposed to γ rays was linear, with effectiveness decreasing as dose protraction was increased.

When the results from these analyses are restricted to conditions (24 once-weekly exposures to γ rays and a 21-cGy maximum dose of neutrons) similar to those of Storer and Mitchell (*4*), the RBE values reported in this paper are consistent with the range of 13 to 22 reported in their study. However, when the data for 60 once-weekly exposures to γ rays for females or the 59-week fractionated exposure for males were used as the baseline, RBE values in excess of 40 were observed for either sex (Table VIII). RBE values of this magnitude are larger than the maximum RBE reported by Storer and Mitchell (*4*) by a factor of 2. The large RBE values resulted from a combination of (i) the inverse relationship between maximum dose considered and life shortening per centigray at low doses of neutron exposure, and (ii) the decreased effectiveness of γ rays as dose was protracted. It should be emphasized that we have simply reported the γ-ray baseline employed without making any judgment as to the appropriateness of this choice in the calculation of RBE values.

Potential nonlinearity of the dose response at low doses of neutrons has no impact on the magnitude of the RBE values reported in this paper. When the power function equations for exposure to γ rays and neutrons are set equal to each other and rearranged to generate the appropriate formula for RBE calculation, RBE is seen to be a function of dose. When the power coefficient for γ rays is larger than the corresponding coefficient for neutrons (as is the case in this study), the RBE value increases as the neutron dose is decreased. Applying this approach to the data from this study resulted in RBE values, at least for males, that were within one standard error of those reported in Table VIII. The degree of correspondence between these two approaches was less satisfactory when applied to the data for females. Good agreement was found for single exposures to γ rays, where the power function approach gave larger RBE values for the 24 once-weekly exposures to γ rays and lower RBE values for 60 once-weekly exposures to γ rays. As reported earlier, the RBE values generated for the Thomson equation (model 6) were nearly identical to those derived from power functions. It appears, therefore, that in the linear or near-linear range of these data, the estimation of RBE values is relatively insensitive to the form of the dose–response equation employed. It should be noted that the augmentation of life shortening observed at 80 cGy and above for neutron exposure also had no effect on the reported RBE values because only slope coefficients derived before the emergence of this effect were used to represent the life shortening for exposure to neutrons in the calculation of RBE values.

The appropriate mathematical form of the dose response for exposure to neutrons is dependent on the dose range selected for analysis, and this choice can have a major impact on the calculation of RBE. When a linear–quadratic equation is inappropriately fitted to the linear range of the neutron data, the resulting RBE estimate may be distorted. Similarly, when a linear equation is employed where the response curve begins to flatten out at higher doses, the linear coefficient will be a poor estimate of the life-shortening response to neutrons at low doses. Even when the entire dose range for neutrons was appropriately modeled by a linear–quadratic equation or a nonlinear model, with adjustments for exposure pattern, the resulting RBE values were lower than those estimated at low doses.

Alternative equations were therefore investigated to determine whether a model could be identified that would be less sensitive to dose range for exposure to neutrons. The dampening-factor models, at least for single exposures, provided significantly better fits than the linear–quadratic equation. As was expected, a dampening factor applied to the linear term in these models increased the estimated days lost per centigray (Table VII) relative to estimates generated from a linear–quadratic model. It should be emphasized, however, that this model was selected from the family of dampening-factor models considered because it significantly reduced the SSE (particularly for single exposures), not because it increased the magnitude of the life-shortening coefficient. This dampening-factor model, when applied to the entire neutron dose range, did provide estimates of the life-shortening coefficient similar to those obtained for the low-dose ranges (maximum dose < 40 cGy) in the truncated data sets (see Tables IV and V). From a statistical point of view, a single model applied to the entire set of data is more satisfying because of the increased sample size and because the problem of nonindependence created by treating the truncated data as independent sets of observations is eliminated.

It was initially thought that a polynomial spline model with an unknown join point might solve the problem of estimating a maximum RBE value. An initial linear fit applied to the low doses of neutrons and a simultaneous linear–quadratic fit applied to the high doses, where a leveling off of response has been observed, seemed reasonable. Further, the join point estimate itself would provide useful information by identifying the dose point at which curvature in the dose response became significant. The observation that the linear–quadratic equation was superior to the spline model (with its initial linear fit) may suggest that existing curvature in the response to neutrons at low doses could not be detected in the analyses of the truncated data. Alternatively, the distribution of available dose points in our data may have prevented the spline model from identifying a linear region (i.e., estimating a join point within the range of the data). In the strict statistical sense, the spline model, by utilizing the entire data set, should have been more powerful than reliance on a progressively smaller number of dose points to test hypotheses concerning curvature. The spline model did not, however, prove effective with these data.

A rigorous determination of the actual shape of the dose response for neutrons at low doses will require either a more extensive data base or one with a different distribution of dose points than the data presented in this paper. In the end, we must agree with our colleagues (*5, 7*) that no single equation appears to adequately describe the dose response for exposure to neutrons in both the low- and high-dose regions. The

results of this study suggest that the dose range used for neutron exposure, not the specific model employed, and the baseline used for exposure to γ rays are the dominant factors influencing the estimation of RBE values. Three final comments are in order: (i) the mathematical models chosen for analysis were strictly empirical and were not assumed to have any biological significance with regard to mechanisms of injury; (ii) no judgment was made concerning which exposure pattern for γ rays should be selected as a baseline for the calculation of RBE values; and (iii) the analyses reported here were entirely retrospective, and the hypotheses addressed were not part of the original intent or design of the experiments. In the field of statistics concerned with the design and analysis of experiments, this final point is not trivial. The ineffectiveness of the spline model, for example, was probably due to the inappropriate array of dose points available for testing this particular model. The individual experiments in the JANUS program were generally designed to compare the effectiveness of γ rays and neutrons at comparable levels of biological injury for reasons of experimental comparative pathology. The requirements in experimental design for these experiments were therefore quite different from those concerned with the subtleties of testing the appropriateness of multiparameter mathematical models.

RECEIVED: July 14, 1988; ACCEPTED: February 24, 1989

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