Paper

CORRECTIONS IN THE ATOMIC BOMB DATA TO EXAMINE LOW DOSE RISK

Gizelle S. Baker and David G. Hoel*

Abstract—**Cancer incidence and mortality data from the cohort of Japanese atomic bomb survivors in Hiroshima have been adjusted for the uncertainty that exists in the dose estimates, the 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 were modeled with a threshold term to allow for the possibility of a threshold dose response. The dose response models that were fit to the data were otherwise the same models used in the original papers. The threshold term was included in the model allowing for possible threshold values ranging from 0 to 0.35 Sv. These analyses suggest that the fit of the A-bomb solid tumor and leukemia incidence data are significantly improved by the addition of a threshold term in comparison with the purely linear or linear quadratic model. The results from the mortality data suggest 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.**
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Key words: atomic bomb; Hiroshima; dose, low; health effects

INTRODUCTION

RADIATION PROTECTION agencies estimate radiation-induced cancer risks based on epidemiological studies of the Hiroshima and Nagasaki A-bomb survivors, medically irradiated patients, and occupational cohorts using the traditional linear no-threshold model. Debates on the scientific basis of the linear hypothesis have appeared in recent literature (Goldman 1996; NCRP 2001). The linear no-threshold assumption has been adopted as a "*pragmatic guideline in the absence of scientific certainty*" because the complexities of cell responses at low doses cannot be resolved with epidemiological studies. Recent observations—such as genomic instability, bystander effect, and adaptive response are complexities that can modify the response at low doses, which if inducible in humans may invalidate some of the arguments that favor the linear no-threshold model (Kellerer and Nekolla 2000).

The Japanese A-bomb survivor Life Span Study (LSS) cohort is the principal dataset used in assessing the cancer risks following exposure to ionizing radiation (UNSCEAR 1994). This population was exposed at high dose rates; therefore, the risk estimates must be extrapolated to derive estimates of cancer risks for the general public and occupational groups who are exposed to relatively low-dose protracted exposures. Models have been developed to extrapolate between high and low doses from both acute exposure and chronic or protracted exposures, and across time (Cardis et al. 2001). The problem is that these models inevitably introduce uncertainty into the estimates and have been the center of debate for many years.

It is generally accepted that high dose, high dose-rate radiation induced cancer data are well described by a linear dose-response, the issue of interest in radiation risk assessment is the shape of the dose-response curve at low-doses. The problem is that non-linearities are almost impossible to observe or rule out at low-doses in epidemiological data (NCRP 2001). This is because the cancer risks at low doses are too small to observe and confounders exist that cannot be controlled for in human populations. There is also the issue of uncertainty and error in the dose estimates and their potential impact on the dose-response curve. Studies have shown that errors in the dose estimates can substantially alter the shape of the dose-response relationship, thereby nullifying any evidence for possible non-linearity in the dose-response (Little and Muirhead 2000). The issue of uncertainty in the Radiation Effects Research Foundation (RERF) data has been investigated (Jablon 1971; Little and Muirhead 1997; Little and Muirhead 2000; Pierce et al. 1990). The presence of random errors in the dose estimates is from the uncertainty that is involved with any dose reconstruction and the bias introduced by the uncertainty in

* Department of Biometry and Epidemiology at the Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425.

For correspondence or reprints contact: G. S. Baker at the above address, or email at tessiegs@alumni.musc.edu.

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the survivors' location results in an overestimation of dose and, in turn, an underestimation of the radiation effect in dose-response analyses (Pierce et al. 1990).

Another issue of concern with the current dose estimates used by RERF is that discrepancies exist between the calculated and the experimental neutron activation measurements. Measurements of thermal (slow) neutron activation products as well as fast neutron activation measurements suggest that a readjustment of the neutron doses is needed (Kellerer and Nekolla 1997; Kellerer and Walsh 2001; Straume et al. 1992). These measurements revealed a systematic underestimation of the neutron component in the dose estimates, especially at smaller doses (survivors beyond 1 km) (Little and Muirhead 2000; Rossi and Zaider 1996). Recent advancements in accelerator mass spectrometry have made it possible to determine the fast neutron fluences in Hiroshima using ^{63}Ni measurements in copper (Ruhm et al. 2000). Preliminary ^{63}Ni measurements have discounted the earlier tentative correction based on slow neutron activation measurements using ^{36}Cl (National Research Council 2001). The unpublished ^{63}Ni activation measurement data are unconfirmed, although the relationship between neutron and gamma doses was discussed by the National Research Council (National Research Council 2001).

The acute effects of neutron exposure are known from radiobiological studies, while their capability to produce late effects such as cancer are not known from human observation. The most reliable information on the late effects of neutron exposure comes from experimental animal studies, but due to the uncertainty in these results this information cannot be directly extrapolated to humans. Since neutrons are the more effective ionizing radiation, a lower absorbed dose of neutrons than gamma rays is needed to produce the same biological effect; therefore, a relative biological effectiveness (RBE) value is used in calculating the cancer risk estimates of neutrons and gamma rays (Edwards 1999). The dose equivalent, measured in Sieverts (Sv), is simply the product of the RBE and the absorbed dose and results in a risk estimate that can be applied equally to the neutrons and gamma rays. The major analyses of the LSS data have assumed a constant weighting factor of 10 or 20 for the neutron RBE, even though radiation biology has shown that the neutron RBE increases with decreasing dose (Rossi and Zaider 1996). The problem is that RBE cannot be extracted with any certainty directly from epidemiological data (Edwards 1999); an attempt to calculate RBE using the A-bomb data resulted in an estimated RBE of 70 ($\pm$50) (Zaider 1991). Rossi and Zaider (1996) and Pierce et al. (1996) present methods using parameters extracted from human lymphocyte aberration data to calculate a dose-dependent RBE that can be applied to the A-bomb data.

Analyses of the unadjusted dose estimates have indicated using linear threshold models (as a surrogate for non-linearity) that the addition of a threshold term significantly improved the linear-quadratic model dose response model for leukemias (Hoel and Li 1998). It has since been suggested that this finding is an artifact of the uncertainties that exist in the dose estimates, and, if they were accounted for, there would be no evidence for a threshold in the linear-quadratic model (Little 1999).

The purpose of this paper is to reinvestigate the threshold dose response models after simultaneously adjusting for the uncertainty in the dose estimates, the systematic underestimation of the neutron component as a function of distance from the hypocenter, and a dose-dependent RBE. Specifically, we will evaluate the models with the a) original uncorrected dose estimates, b) doses corrected for both the uncertainty and systematic error in the neutron dose estimates (using the new fast neutron activation measurement) with either a fixed (RBE = 10) or c) a dose-dependent RBE.

MATERIAL AND METHODS

The study population

The data being used in these analyses are the publicly available cancer incidence and mortality data of the RERF's LSS cohort with doses less than 4 Gy. The solid tumor incidence data include the 79,972 survivors of the cohort who were alive as of 1 January 1958. The solid tumor cases were determined by matching the survivor data with the Hiroshima and Nagasaki Tumor Registry—as of 31 December 1987, a total of 8,613 cases were found (Mabuchi et al. 1994; Thompson et al. 1994). The leukemia incidence data includes 86,293 survivors who were followed from 1 October 1950, through the end of December 1987, matched with the Leukemia Registry for a total of 339 leukemia cases (Preston et al. 1994). The most recent mortality data has an extended follow-up through 1990 and uses death certificate data for cancer mortality—this cohort includes 86,572 survivors with 7,578 cases of cancer, including 249 cases of leukemia (Pierce et al. 1996b).

Statistical methods

These analyses have been restricted to the Hiroshima population because the uranium bomb resulted in a considerably larger neutron component of exposure to this population. Poisson regression methods similar to those used in the original studies by Preston et al. (1994) and Thompson et al. (1994) are used in the following analyses. This approach divides the data into cells based

on city, sex, age-at-exposure, follow-up time, and weighted organ doses. Using Poisson regression models for cancer incidence assumes that the number of cases in each of the cells is a Poisson random variable with the mean and variance equal to the product of the person years at risk (PYR) and the incidence rate. AMFIT (Preston et al. 1991) is used to fit the model to the data, calculating the deviance as a measure of the goodness of fit. The deviance is distributed approximately χ^2 with degrees of freedom equal to the difference in the number of cells and the number of parameters included in the model. The addition of a threshold term significantly improves the models if the deviance is reduced by a value greater than the critical value of a χ^2 distribution with 1 degree of freedom (3.84 for alpha = 0.05).

The general class of models for the solid tumor incidence, $\lambda(D)$, and the subtypes of solid tumors are of the form

$$\lambda(D) = \lambda(c,s,a,y) \times [1 + \mathrm{ERR}(D,e,s,a)], \quad (1)$$

where $\lambda(c, s, a, y)$ is the background incidence rate that depends on city (c), sex (s), attained age (a), and year (y). The other term in the model is the excess relative risk (ERR), which is modeled as a function of the true total dose (D), where the total dose is made up of the dose of gamma rays (D_γ) combined with the product of an RBE value and the neutron dose (D_n), age-at exposure (e), sex (s), and attained age (a).

The leukemia incidence models are similar but are modeled using excess absolute risk (EAR):

$$\lambda(D) = \lambda(c,s,a,y) + \mathrm{EAR}(D,e,s,t), \quad (2)$$

where t is the time since exposure. The models used in these analyses are those used in the original studies for solid tumor incidence by Thompson et al. (1994), leukemia incidence by Preston et al. (1994), and mortality by Pierce et al. (1996).

Dose thresholds are added to a model of $\lambda(D)$ by defining the cancer rate as

$$\begin{aligned} \lambda(D|d_0) &= \lambda(D - d_0) \text{ for all} \qquad D > d_0 \\ &= \lambda(0) \text{ for all} \qquad D < d_0, \end{aligned} \quad (3)$$

where d_0 is the given threshold dose (Hoel and Li 1998).

The gamma and neutron doses (d_γ and d_n) available in the data are estimated doses because the true doses (D_γ and D_n) are not known. It has been shown that by replacing $\lambda(D)$ with the average $[\lambda(D|\, d)]$ in fitting the model

$$avg[\lambda(D_\gamma,D_n|d_\gamma,d_n)] = \lambda(c,s,a,y) \times [1 + \mathrm{ERR}(D_\gamma,D_n,e,s,a)], \quad (4)$$

the parameter estimates are approximately unbiased (Pierce et al. 1990; Little and Muirhead 2000). This method is comparable to the methods used by Pierce et al. (1990) and Little and Muirhead (1997, 2000). In this analysis, the errors in the neutron and gamma dose estimates are accounted for separately, similar to Little and Muirhead (2000), where the parametric form of the true dose is the probability of a true dose exceeding any value D and is given by the Weibull distribution $\exp(-\theta_1 D^{\theta_2})$. The parameters θ_1 and θ_2 are found for each combination radiation type, so that the resulting distribution matches that of the estimated doses (Pierce et al. 1990; Pierce et al. 1991). The distribution of the estimated dose given the true dose, $f(d|D)$, is assumed to be log-normal with median D and coefficient of variation d, which is approximately equal to the standard deviation of $\log(d)$. A log-normal model with a geometric standard deviation (GSD) of 30% to 40% was suggested based on the nature of the major sources of uncertainty in the dose estimates (Jablon 1971). The results in this paper are based on the log-normal 35% error model.

Since the DS86 neutron dose estimates may be systematically underestimated, a tentative correction was used to bring the neutron doses in line with the measurements of activation by the slow neutrons. The work from Straume et al. (1992) and Kellerer and Nekolla (1997) suggests the following relationship:

$$d_n^c = C(r)d_n, \quad (5)$$

where d_n^c is the corrected mean neutron dose and $C(r)$ is the correction factor, which is a function of the distance (r) from the hypocenter of the bomb, measured in kilometers. Since the RERF data set does not contain data on distances from the hypocenter, they must be inferred from the relationship between dose and distance as given in Table 40 of Kerr et al. (1987) and the mean shielding factors given in Pierce et al. (1996a). The relationship between gamma dose and distance is less dependent on the shielding than the neutron dose (Kellerer and Nekolla 1997) and therefore is used as the surrogate for distance in the correction factor $C(r)$. We used very similar methods in calculating a correction factor to bring the neutron doses in line with the fast neutron measurements. This correction is shown for Hiroshima as the ratio of the neutron to gamma dose in Fig. 1.

The importance of a dose-dependent RBE in analyzing the A-bomb data is another issue that has been debated. Although most studies have applied dose-independent RBE's, radiation biology suggests the need for a dose-dependent RBE (Rossi and Zaider 1996),

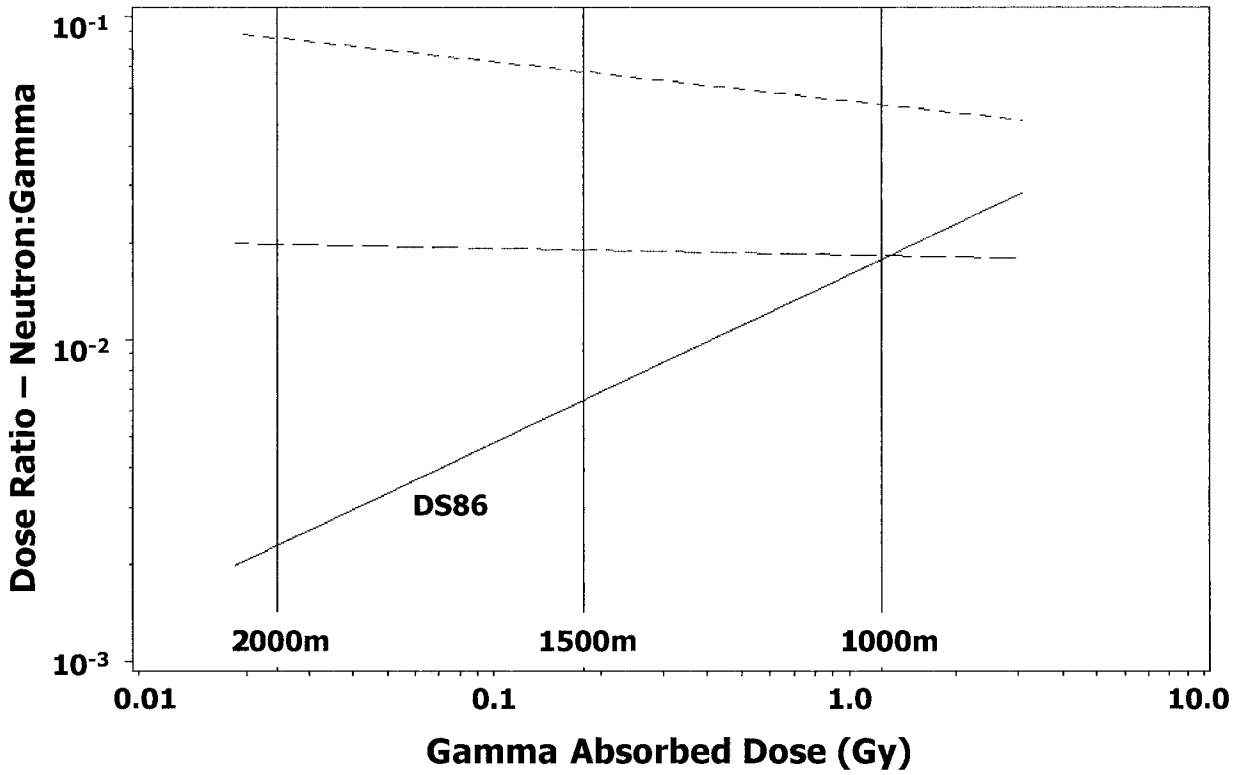

Fig. 1. Plot of the ratio of the neutron to gamma absorbed dose vs. the gamma absorbed dose for Hiroshima. The doses used are average organ doses, which are equivalent to the marrow doses (Kellerer 2001). The current dosimetry, the DS86 is given as (—); the estimates based on the slow neutron activation measurements (^{36}Cl) represented by (- - -) (Straume 1992); (— — —) represents the estimates based on an intermediate adjustment that is consistent with the available ^{63}Ni measurements from Hiroshima (National Research Council 2001).

which can be calculated from human lymphocyte chromosomal aberration data (Edwards et al. 1980). Since the exposures in Hiroshima and Nagasaki were a combination of gamma rays and neutrons, both doses must be used in calculating the neutron RBE. Using the assumptions of Rossi and Zaider (1996) and the equation for an RBE of mixed exposure from Pierce et al. (1996):

$$RBE(D_\gamma, D_n) = \frac{\alpha_\gamma}{2\beta_\gamma D_n} \left[-\left(1 + \frac{2\beta_\gamma}{\alpha_\gamma} D_\gamma\right) + \sqrt{\left(1 + \frac{2\beta_\gamma}{\alpha_\gamma} D_\gamma\right)^2 + \frac{4\beta_\gamma \alpha_n}{\alpha_\gamma^2} D_n} \right], \quad (6)$$

where $\alpha_\gamma = 1.57 \times 10^{-2}$ Gy^{-1}, $\beta_\gamma = 5.00 \times 10^{-2}$ Gy^{-2}, $\alpha_n = 83.5 \times 10^{-2}$ Gy^{-1}, and $\beta_n = 0$, we can calculate an approximate dose-dependent RBE for each dose. In the RERF data sets, small neutron doses (less than 0.001 Gy) are set equal to zero. This problem does not affect risk estimates when the typical RBE values of 10 and 20 are used in calculating dose; however, it has been shown that when the RBE is dependent on dose the smaller doses result in larger RBEs and the problem becomes appreciable. To fill in the missing values of neutrons, a combination of the mortality and incidence data was used to determine the average overall relationship between the neutron dose (d_n) and gamma dose (d_γ), before and after the fast (^{63}Ni) and slow (^{36}Cl) neutron activation measurement corrections were made to the neutron dose estimates, shown in Fig. 2. This relationship was then used to replace the percentage of the missing values that corresponds to survivors whose doses were set equal to zero (the cohort also included an essentially unexposed group sample beyond 3 km) (Pierce and Preston 2000).

RESULTS

Solid cancer

In Table 1, the RBE values are calculated for the corrected (adjusted for dose uncertainty and error in the neutron doses) and uncorrected doses and given as an average for each dose group. A ratio of the average dose, with a variable RBE to those with a constant RBE of 10, is given to illustrate the effect of the variable RBE on the

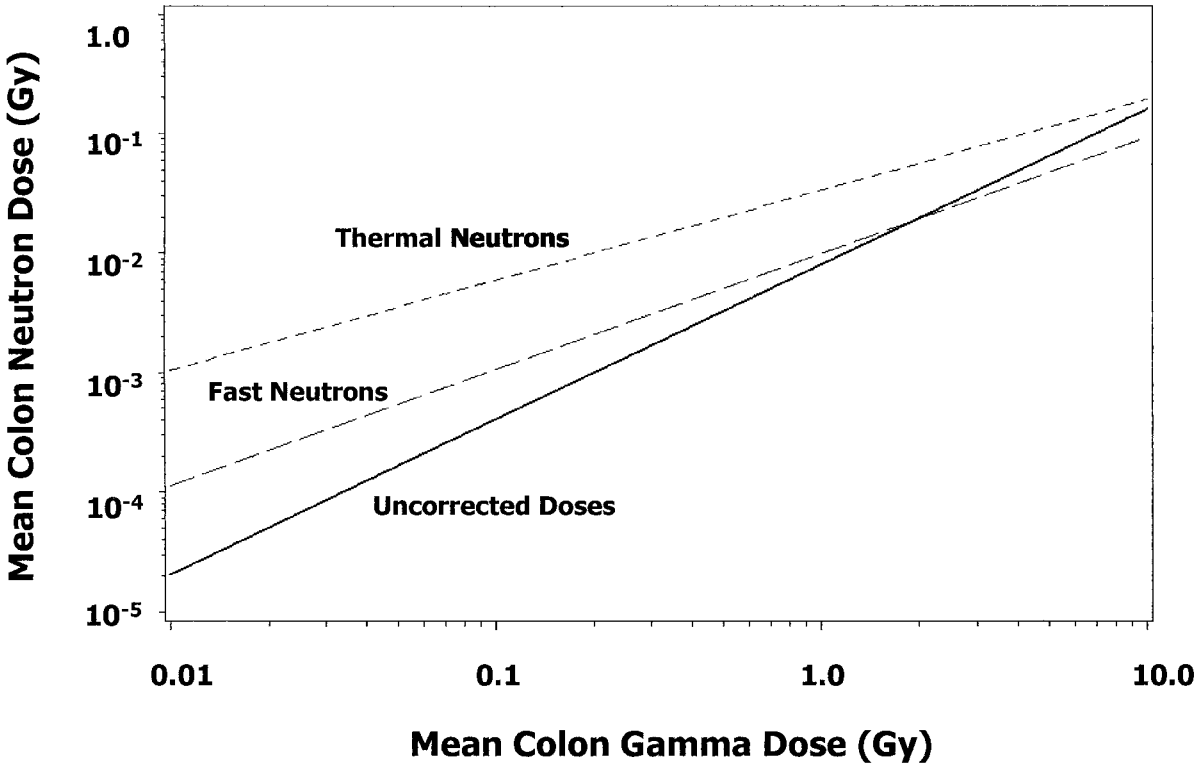

Fig. 2. The mean neutron doses vs. the mean gamma ray doses to the colon in the RERF datasets for cancer mortality and incidence (Hiroshima). The solid line represents the uncorrected doses that are available in the data, the dotted line (- - -) represents the correction for the slow neutrons (^{36}Cl) combined with the uncertainty correction while the dashed line (— — —) represents the fast neutron correction (^{63}Ni) combined with the uncertainty correction of the doses.

Table 1. Estimated average RBE values and ratio of the variable RBE dose to the fixed RBE (=10) dose for weighted dose groups using the corrected and uncorrected doses.

Weighted dose (Sv)		<0.10	0.10–0.25	0.25–0.50	0.50–1.0	1.0–1.5	1.5–2.0	>2.0
Uncorrected	RBE	46.0	27.6	17.4	10.0	6.1	4.6	3.5
	$\frac{\text{Dose}_{RBE(Var)}}{\text{Dose}_{RBE(10)}}$	1.07	1.07	1.03	1.00	0.97	0.95	0.94
Corrected	RBE	45.2	26.5	16.9	10.1	6.3	4.7	3.7
	$\frac{\text{Dose}_{RBE(Var)}}{\text{Dose}_{RBE(10)}}$	1.46	1.25	1.12	1.03	0.96	0.94	0.91

total weighted dose, where the weighted dose is calculated as $d_\gamma + RBE(d_\gamma,d_n)d_n$. The effect of a variable RBE is an increase in the estimated doses for doses originally less than one Sv and a decrease in the dose estimates for those greater than 1 Sv. This finding is more dramatic for the low dose groups once the adjustments for uncertainty and error have been incorporated.

In the original analysis of solid cancer incidence by Thompson et al. (1994), the data were adjusted for city, sex, age-at-exposure, and calendar time, with the excess relative risk assumed to be linear in dose and modified by sex and age-at-exposure. The background risk of cancer is modeled parametrically with a log linear function of city, sex, year of birth, log age, and log age squared. Hoel and Li (1998) observed that the fitted dose response curve underestimates the number of cancers in the zero dose group while overestimating the lowest exposure group (0.01 to 0.1 Sv), as one would expect in the case of low dose non-linearities. These calculations suggest the possibility of non-linearities in the low dose region of the dose response curve; therefore, a dose response curve that incorporates a linear threshold term was fit to the solid incidence data. In Fig. 3, the change in deviance score from the linear no threshold model vs. the model's threshold dose are plotted. Three types of dose values are considered: the uncorrected original dose, doses corrected for uncertainty and error with a fixed RBE value, and corrected doses with a dose dependent RBE. We

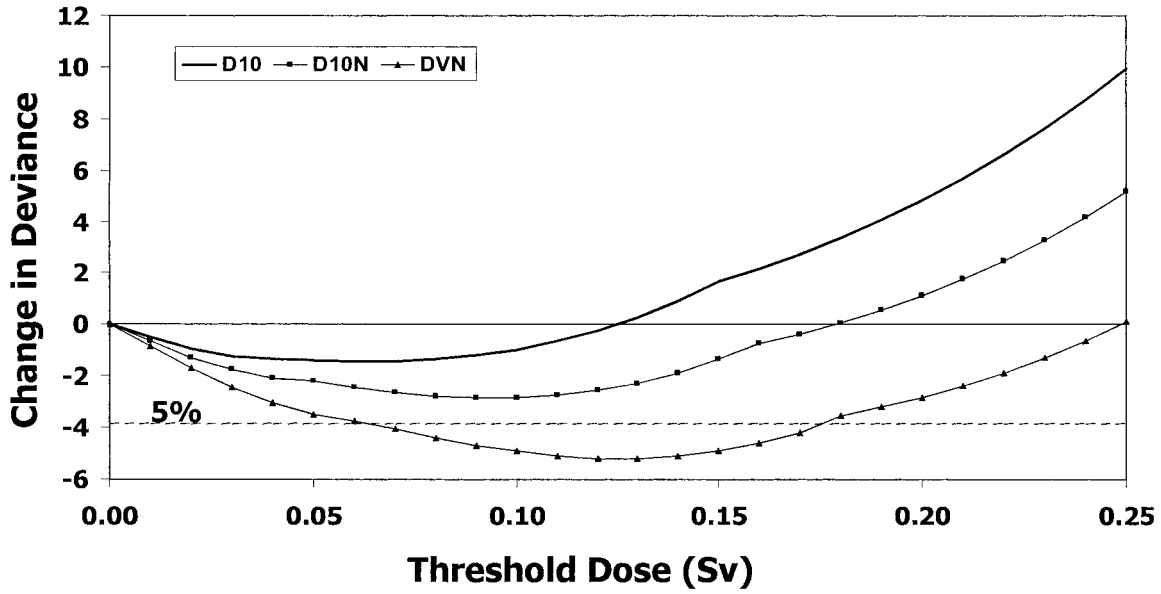

Fig. 3. Plot of the change in statistical deviance from a no threshold model vs. the model's threshold value are given for solid tumor incidence. The smaller the deviance value the better the model's statistical fit to the data—therefore, the large negative changes in deviance indicate that the threshold model fits the data better than a no threshold model. The horizontal line indicates when the change in deviance is significantly better ($p = 0.05$) than a no threshold model. D10 is the uncorrected colon dose estimates available in the solid tumor incidence data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

observe that with uncorrected doses and fixed corrected doses, a threshold up to 0.1 Sv appears to improve in the models fit, although there is no significant difference between the linear and threshold models. In the case of the variable corrected dose, the threshold provides a significant improvement in the fit of the model at doses between 0.07 Sv and 0.17 Sv.

Models of solid tumor mortality give a different picture. In the paper by Pierce et al. (1996b), cancer mortality is modeled using a stratified background and an excess relative risk that is linear in dose and dependent on sex and age-at-exposure. We see that the addition of a threshold term offers no improvement in the fit of the model, but threshold doses up to 0.15 Sv are not statistically worse from the no threshold model, shown in Fig. 4, where the change in deviance is plotted for the three different dose estimates as a function of the threshold dose.

Leukemia

Data on leukemia incidence from Preston et al. (1994) were used to examine the dose response curve for total leukemias. At doses less than 0.30 Sv the linear no-threshold model based on the doses available in the RERF data overestimates the risk of leukemia predicted from the corrected doses and threshold models. A threshold term was incorporated into the models as was done with solid tumors. Fig. 5 shows the change in the fitted deviance values plotted vs. the threshold doses used in the model. In the cases of leukemias, we see an improvement in the fit of the model with the addition of a threshold. The threshold model provides a statistically better description of the data than is seen with the no threshold model for threshold values up to 0.15 Sv with the uncorrected doses and fixed corrected doses and up to 0.2 Sv for the variable corrected doses. The results of adding a threshold for the subtypes leukemia were similar to the results for the uncorrected doses presented in Hoel and Li (1998). ALL and CML were fit with a dose response function linear in dose while AML and total leukemia were fit with a linear-quadratic function. For CML the threshold model provided a significantly better description of the data than the no-threshold model, while the addition of a threshold for ALL and AML indicated an improvement in fit that was not statistically better than the no-threshold model. The original, uncorrected doses (D10), as well as the doses corrected for the uncertainties in the dose estimates and the systematic error in the neutron estimates (with a fixed RBE of 10 "D10N" as well as the variable RBE "DVN") have been fit with a linear-quadratic dose function as shown in Fig. 6. We see that the effect of the dose corrections indicate a noticeable difference in the risk estimates even in the low dose region of the curve.

The leukemia mortality data come from the same paper as the solid tumor mortality by Pierce et al. (1996b), but the leukemia models are more complicated. Leukemia mortality is modeled using a parametrically

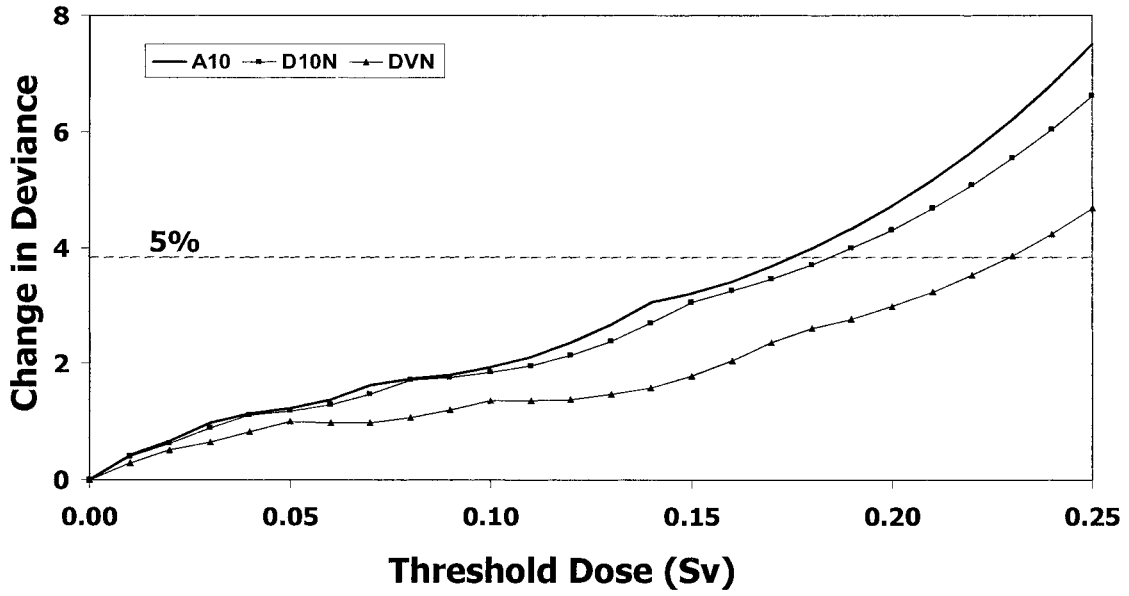

Fig. 4. Plot of the change in deviance vs. threshold dose similar to Fig. 1 for solid tumor mortality. A10 is the adjusted colon dose with a fixed RBE of 10 that is given in the mortality data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

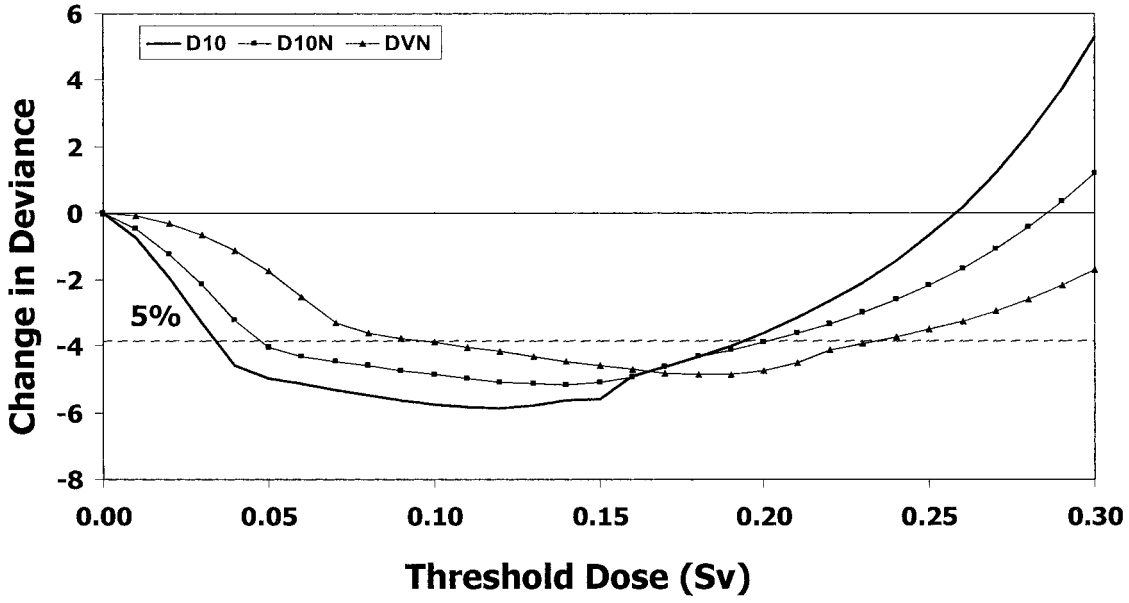

Fig. 5. Plots of the change in deviance vs. threshold dose similar to Fig. 1 for leukemia incidence data. D10 is the uncorrected marrow dose with a fixed RBE of 10 that is given in the leukemia incidence data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

modeled background and an excess additive risk component that is linear-quadratic in dose and modified by sex, age-at-exposure, and time since exposure. The change in the fitted deviance values is plotted against the threshold doses for leukemia mortality in Fig. 7. Although we see an improvement in the fit of the model with a threshold, similar to the leukemia incidence models, the improvement is not significant for the leukemia mortality data.

DISCUSSION

These analyses have shown that the A-bomb survivor data for radiation-induced cancers (solid tumors and leukemias) are consistent with a non-linear dose response model. These findings have been seen with the current dosimetry, as well as with the doses that incorporate information about the uncertainty in the dose estimates, a

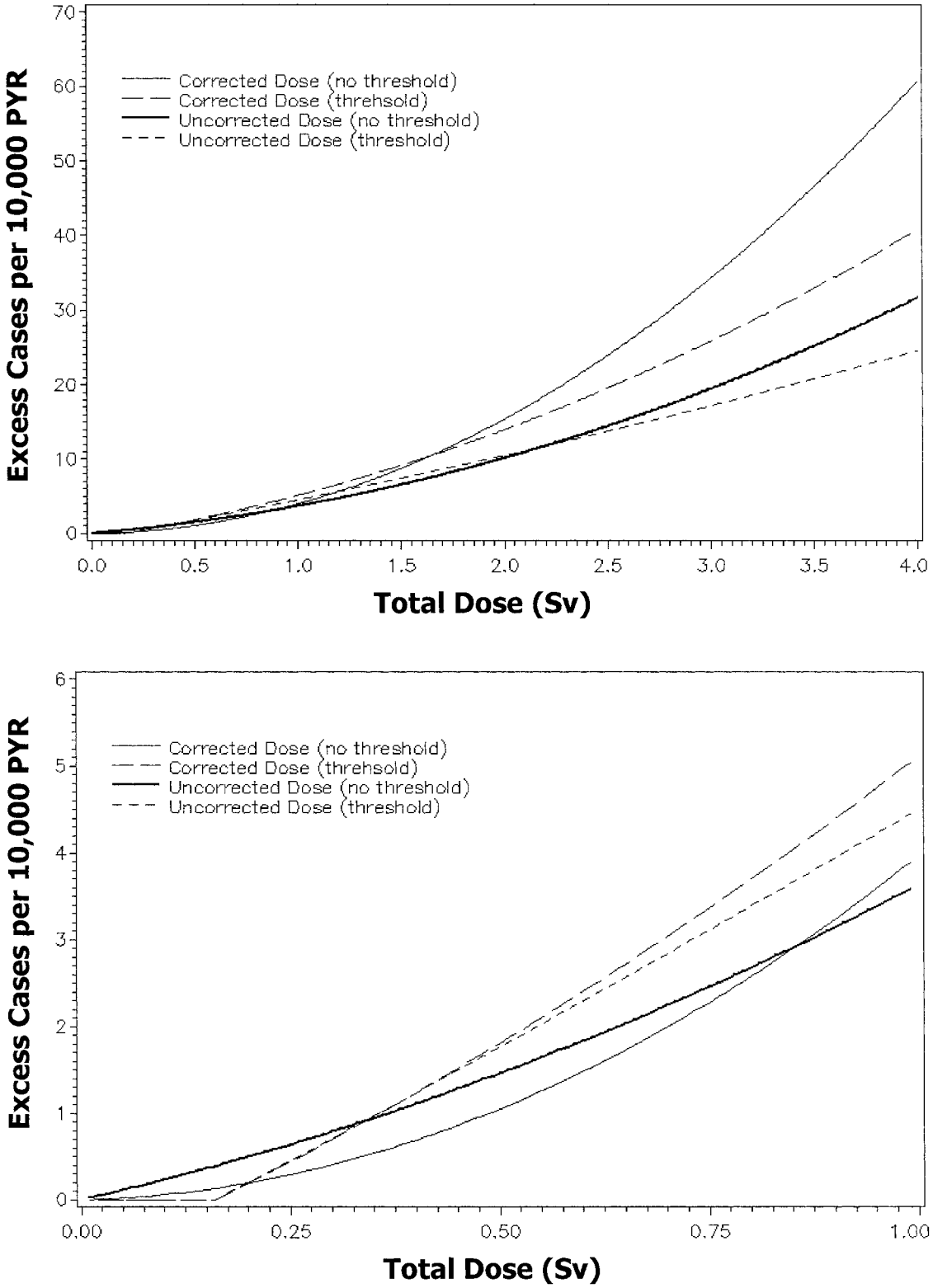

Fig. 6. Dose response curve for leukemia incidence in Hiroshima. Plot of the excess absolute risk of leukemia as a function of dose for males that were 20–39 y old at the time of bombing, 10 y after the exposure. The lower figure depicts the effects of the different models and dose correction at low doses.

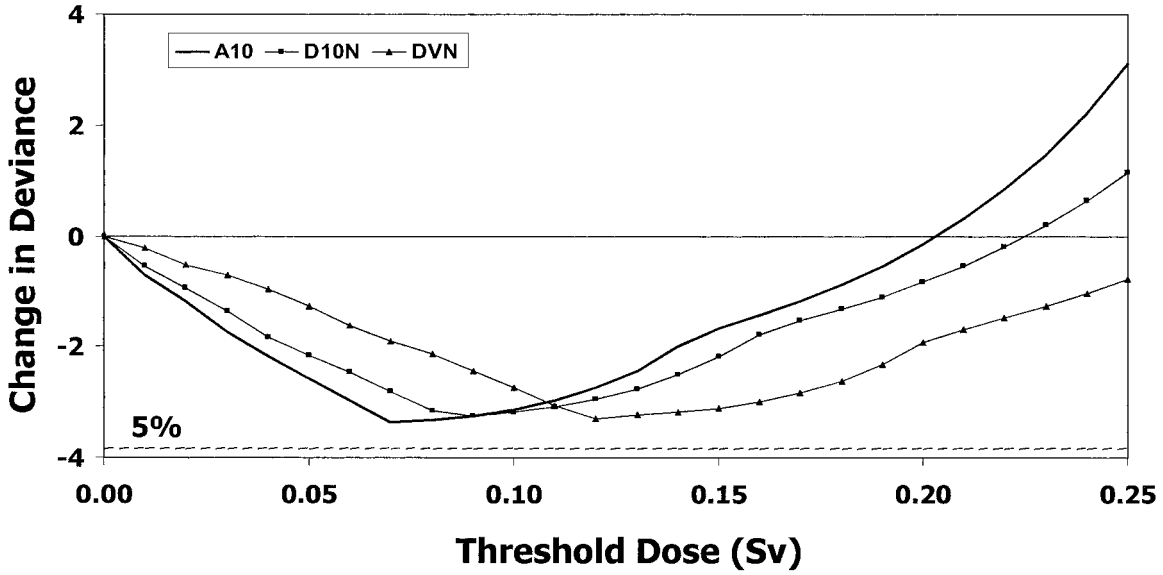

Fig. 7. Plots of the change in deviance versus threshold dose similar to Fig. 1 for leukemia mortality. A10 is the adjusted marrow dose with a fixed RBE of 10 that is given in the mortality data, D10N is the fixed corrected dose estimates, and DVN is the variable corrected dose estimates.

correction for the systematic error in the neutron estimates, and the incorporation of a RBE value that corresponds with current radiobiological knowledge. The threshold levels that are estimated depend on the range of doses included in the analysis and the dose estimates (corrected vs. uncorrected dose estimates) that are used. For solid tumor incidence, the incorporation of the uncertainty and error corrections indicate a more pronounced improvement in the fit; furthermore, when a variable RBE term is added, the threshold model results in a significantly better fit with an optimal threshold value of between 0.10 and 0.15 Sv—in the case of the leukemia incidence data, the results were the opposite. The uncorrected dose resulted in the most significant improvement with a threshold of about 0.1 Sv, the fixed corrected doses were less significant but with approximately the same threshold, and the variable corrected doses resulted in the least significant improvement but with a threshold of about 0.17 Sv. The results from Little and Muirhead (2000) used a fixed RBE model (RBE = 20) while correcting for uncertainty in the dose estimates and bringing the neutron estimates in line with the slow neutron activation measurements and indicated similar findings to the results in this paper for a fixed RBE (RBE = 10). In their analysis the corrected doses suggest an appreciable, although not statistically significant upward curvature with the solid tumor incidence data, while the leukemia incidence data indicated a reduction in the significance of the curvature. In these analyses with a fixed RBE, the threshold becomes more significant for solid tumor incidence, although it does not reach statistical significance until the variable RBE is incorporated; while the threshold model for the leukemia data remains statistically significant, the significance of the threshold is reduced.

Since this study assumes a linear dose response relationship with and without a threshold, the behavior modeled at the lower doses can be greatly impacted by the data at higher doses. To investigate the effect, the analyses were repeated on a low dose subset of the solid tumor and leukemia incidence data, where only doses up to and including 0.5 Sv were included in the analysis. Although none of the results were statistically significant, the solid tumor incidence data showed a similar pattern to the analyses with doses up to 4 Sv. The corrected doses with a variable RBE suggest an appreciable upward curvature. This is not the case with the leukemia incidence data where there is no noticeable improvement in the fit with the addition of a threshold term in the model. This later finding may be due to the fact that below 0.2 Gy no increase in leukemia is seen but below 0.5 Gy there is an increase in leukemia but it is limited with regard to differentiating between models.

Multiple imputation (Rubin 1987) is a popular statistical method used with missing data or data measured with error, and we applied multiple imputation methods to impute the true dose given the nominal dose for the solid tumor incidence data. A lognormal model was used to impute the true dose given the nominal dose, and 50 multiple imputation datasets were performed. The

multiple imputation estimates and standard error estimates were very similar to those obtained using the corrected doses. In particular, using multiple imputation, $\bar{\beta}_{dose} = 1.198$ (estimated standard error 0.3721); using the corrected doses, $\bar{\beta}_{dose} = 1.186$ (estimated standard error 0.3676). Thus, the similarity of the estimates from these two methods suggests that using the corrected doses will produce unbiased estimates.

The cancer mortality data did not indicate an improvement with the addition of a threshold and appears to be inconsistent with the observation of non-linearity in the low dose region of the dose response curve, even with adjustments for the suggested errors in the doses. This could be due to a bias introduced due to urban-rural differences. Pierce and Preston (2000) observed that the distal group (more than 3,000 m from the hypocenter) has about a 5% higher cancer mortality rate than estimated for the zero dose group from the proximal survivors. Although the bias is small, it can substantially affect the assessment of risk at low doses.

Other studies have been used to assess the effects of low dose radiation in the production of cancers. A study of cancer mortality in a cohort of Canadian fluoroscopy patients, fractionated exposures to low LET radiation resulted in a decreased lung cancer mortality than would be expected at the same dose from the A-bomb data (Howe 1995), while the risk of breast cancer mortality was not affected by fractionation (Howe and McLaughlin 1996). There are problems with the direct comparability of these previous studies that have to be taken into account in interpreting our results. The exposure in A-bomb survivor data is the result of an acute exposure to radiation, while the majority of human exposure to ionizing radiation is low dose, low dose-rate exposure which can result in different mechanisms and therefore different and more complicated dose-response curves.

Experimental animal studies have also provided information regarding the effect of dose rate on the induction of cancers and have resulted in the recommendation of a dose rate effectiveness factor (DREF) between 2 and 10 for low doses of low LET radiation (Committee on the Biological Effects of Ionizing Radiation 1990). If the effectiveness of radiation is reduced when the exposures are protracted, the result could be an effect of non-linearity at low doses.

Occupational studies of radiation workers have also provided information on the issue of linearity at low doses. However, when total doses are low, occupational data do not provide clear evidence of risk because the precision of these studies is limited by the data and, with small exposures, there is the possibility of masking the radiation effect with the "healthy worker effect" that is often associated with occupational studies (Cardis et al. 2001). The curvilinear dose response relationship found for leukemia in the A-bomb data indicates no noticeable risk at doses below 0.20 Sv. Most occupational studies with low cumulative doses have also shown no excess risk of leukemia at low doses, although there are some exceptions. Cardis et al. show that excess risks of leukemia in occupational studies are usually associated with dose greater than 0.4 Sv. The problem with these studies, as with most epidemiological studies of radiation exposure is that they suffer limitations, which impact the interpretation of the data and may make the capability of resolving the issue of low dose risk beyond the capability of epidemiological data alone.

The scientific basis for the no-threshold model comes from scientific studies of mutagenesis, and clastogenic and chromosomal aberrations. Mutation frequencies have been shown to increase with either linear or linear-quadratic dose response curves, depending on the radiation quality, LET of the radiation, dose rate, and genetic background of the cell. In either case, there is no direct evidence of a threshold; therefore, if cancer formation is directly related to mutation induction the data do not support a threshold in the cancer dose response, but one cannot rule out a nonlinear dose response. Chromosomal studies can only lead to predictions of a threshold if DNA repair is error free at low doses, but the existing data cannot support or refute these predictions. Although a linear no threshold model fits cellular data for many biological alterations that may be precursors for cancer, as well as the epidemiological data, it is important to note that they do not provide evidence that low dose non-linearities or threshold are absent in the data. Further, the discovery of issues such as genomic and chromosomal instability, bystander effects, and adaptive response are currently changing our understanding of radiobiology and must be examined further to comprehend the effects they have at low doses.

CONCLUSION

The main conclusion that can be made from these analyses is that even after adjustments are made for uncertainty associated with the dose estimates, systematic error in the neutron estimates and a dose-dependent RBE, a threshold like dose response, is still consistent with the A-bomb cancer and leukemia incidence data, reinforcing the findings of Hoel and Li (1998) who found similar results using the uncorrected original doses. And although a linear no-threshold model fits the data, it does not provide evidence against low-dose non-linearities or threshold models. The shape of the low dose response curve is an important issue in radiation protection that cannot be resolved with statistics and epidemiology; it

will require a better understanding of the radiation biology at low doses and the effects on radiation carcinogenesis.

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