ANALYTICAL APPROACHES TO AND INTERPRETATIONS OF DATA ON TIME, RATE, AND CAUSE OF DEATH OF MICE EXPOSED TO EXTERNAL GAMMA IRRADIATION

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ANALYTICAL APPROACHES TO AND INTERPRETATIONS OF DATA ON TIME, RATE, AND CAUSE OF DEATH OF MICE EXPOSED TO EXTERNAL GAMMA IRRADIATION*

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Abstract

ANALYTICAL APPROACHES TO AND INTERPRETATIONS OF DATA ON TIME, RATE, AND CAUSE OF DEATH OF MICE EXPOSED TO EXTERNAL GAMMA IRRADIATION.

Young adult male and female mice of inbred strains, A, BALB/c, C57BL/6, and C57L, and $B6CF_1$ and F_2 hybrids were exposed to daily duration-of-life external ^{60}Co γ-irradiation. Age at death was recorded, and most decedents were necropsied to ascertain occurrence of major types of tumors. Age- and cause-specific mortality or incidence rates were derived, and their regressions on age were fitted with polynomial equations by least-squares procedures. Age-specific and age-adjusted integrated lifetime risk in excess of the control population was expressed as the mortality ratio (irradiated/control). Linear and nonlinear functions and widely different life expectancies can be accommodated by this technique. These basic actuarial statistics provide a means for comparative analysis of dose-response functions, sex and genetic variables, relative vs. absolute risk, protraction or dose-rate factors, and major contributing causes of excess risk. They also provide a basis for extrapolation to man.

As examples, life shortening in days per rad (4 days/100 rads accumulated) is generally independent of sex, genotype, and daily dose rate. The integrated average lifetime risk of death related to all tumors (0.025%/rad) is largely independent of sex, genotype and dose-rates < 12 rads/day, despite the fact that tumor incidence varies by a factor of 2 to 3 among genotypes. At low exposure rates, tumor-related mortality accounts for 80% of

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the excess risk, and life shortening is a function only of accumulated dose, independent of dose rate below 12 rads/day. The radiobiological effectiveness for low daily exposure levels is less than that for single exposures by a factor of 5 to 10. Life shortening following low daily exposure rates is induced at the rate of .03-.06 days/R for the mouse, which extrapolates to about 1-2 days/R for man.

INTRODUCTION

The questions remaining to be answered in the field of applied radiobiology are the motivation for this symposium. Two of the questions of paramount concern have interested us for many years:

1. What are the dose-response functions for the important pathological sequelae of man's exposure to continuous low intensities of external radiation for major portions of the lifetime?
2. How can we best employ and exploit the extensive data from the exposure of experimental animals for extrapolation to man, especially for those issues wherein human statistics are particularly inadequate?

These and similar questions have stood for an embarrassingly long time, even though many of us were confident they should be soon answered, as they did not lack for attention. Any complete annotation of the efforts of individuals and of research groups, let alone national and international committees, that have concerned themselves with these issues would require an historical compendium. The previous symposium of this series [1] is a partial catalogue, to which one can add the recent efforts of the United Nations [2], the U. S. National Research Council - National Academy of Sciences [3], and a small but comprehensive review held in Chicago [4].

The active research groups have been characterized by their selective interest, usually in only one species and in limited biological end points, methods of exposure, and analytical tools. There is little consistency beyond the use of dogs and mice for most work. Before the appearance of the JANUS biomedical research reactor [5] on our experimental scene, our interests at Argonne focused on lifetime exposures, life shortening, and life tables, with the mouse as species of choice.

The rationale was straightforward then and still is. The mouse is economical to use and has many attributes in common with man. The duration-of-life exposure regime (usually commencing at young adulthood) most nearly duplicates any anticipated excess exposure of the general population or the work force. The end point is unequivocal, and the analytical approach recognizes the underlying mixture of predetermined and random forces of mortality characteristic of all mammals.

The basic methods were presented by Sacher in 1950 [6] and by Brues and Sacher in 1952 [7]. They were further developed and applied to radiation lethality data by Sacher [8,9,10] and Grahn [11,12] and also to the consideration of other problems in natural aging [13,14]. We have also extended the analysis to specific causes of death, or to lesions associated with the event of death [7,11,12]. Many features of the experimental data have been summarized in the referenced reports, or in others to be noted. However, there are special analytical applications that have not yet been fully documented, and

our unique body of data, from more than twenty years of research, can continue to be used to demonstrate basic approaches to the analysis of present-day problems in environmental toxicology. We also continue to believe that our basic methods offer a comprehensive approach to the questions stated above.

MATERIALS AND METHODS

We employed a variety of inbred strains of laboratory mice and selected F_1 and F_2 hybrids. The inbreds were the strains A/J, BALB/cJ, C3Hf/He, C57BL/6J, and C57L; the hybrids were the LAF_1 (C57L x A/J), $B6CF_1$ (C57BL/6J x BALB/cJ) and the $B6CF_2$. Generally, both sexes were used in equal numbers. The mice were irradiated beginning at about 100 days of age.

The mice were placed three to a cage at an assigned position in the low-intensity ^{60}Co gamma radiation facility [15] where they received a specified daily exposure until death. Exposures of 8 to 12 hours duration took place during the night so that routine animal care and observation could be provided during the normal work day, and so that the basically nocturnal mice would be exposed during their normal "work day."

Animals were housed in one-liter cylindrical transparent bakelite cages offering free access to food and water, and with wood shavings as litter. Controls were similarly housed and kept in the shielded entry maze of the radiation facility.

The daily dose levels of concern for this discussion were 0, 0.3, 1.3, 2.6, 5/6, 12, 24, 32, 43, and 56 roentgens per day. Dose rates in R/min would change as exposure time was adjusted for source decay, but on the average they were equal to $\frac{\text{R/day}}{\sim 600 \text{ min/day}}$. Thus, the rates ranged between 0.5 and 95 mR/min. The roentgen to rad conversion factor for these experimental conditions is 0.90 [16].

Day of death was determined precisely, and 70% to 90% of the mice were necropsied to obtain the incidence of the major neoplastic, degenerative, and infectious diseases. Only about one-half of those autopsied underwent microscopic study. The identified causes of death include tumors of the reticular tissues, primary pulmonary tumors, ovarian tumors and cysts, hepatomas, and degenerative renal lesions. In addition, a miscellaneous group of tumors, including those of the mammary, adrenal, and connective tissues were added when defining the "deaths from all tumors" category. (The actual cause of death is often difficult to ascertain in the mouse, and our delineation of the age-specific and cause-specific mortality rates is shorthand for a more correct term "age-specific mortality with the lesion of interest.")

The mean after-survival (MAS) data, from the day of initial exposure to death, and derived for each sex, strain, and daily dose group provide the initial analysis and a first basis for extrapolation to man. Age-specific death rates are a focal point of the analyses, however. Populations of mammals die at an exponentially increasing rate with increasing age after the juvenile period. Because the rate is constantly changing, it is ideally estimated over only brief time periods, so that

$$r_t = \frac{D_t}{N_t},$$

where r_t is the death rate for time interval t and D_t is the number of deaths occurring in the interval, and N_t is the number of animals alive at the beginning of the time interval. For small intervals, this reduces to the classical expression of death rate given by many authors [11,17,18],

$$r_t = \frac{1}{N_t}\frac{dN}{dt} .$$

For practical calculations, r_t can be approximated by the expression

$$r_t = (\ln N_t - \ln N_{t+d})/d$$

where d is the number of days in the interval [9,10]. The array of age-specific death rates when plotted as ln r_t vs. age generally conforms to a positive linear function that can be routinely fitted by least-squares regression techniques to yield the constants r_o and k in the exponential equation,

$$r_t = r_o e^{kt} ,$$

the Gompertz equation [9,18,19]. Although r_o is algebraically the intercept at zero age, we have usually set this intercept at 100 days of age, the time of first exposure. In addition, 100 days of age is the approximate time of minimum death rate in the population, or cohort.

The death rates can also be calculated for any specific cause of death, rather than all causes, in which case the equation becomes [11]

$$r_{t_s} = \ln\left[1 - \frac{n_s}{N_t}\right]^{-1} \Big/ t ,$$

where n_s is the number dying of the specific cause in age interval t. The cohort or dose group can also be decremented for any specific cause by eliminating those cases from the number dying and the number at risk at the beginning of the age interval in which the specified deaths occur. This is an especially useful procedure for removal of deaths that fall in a distinctly nonlinear pattern, such as those from reticular tissue tumors, for example, thus permitting a more rigorous linear analysis of the death rate regressions [11,12].

Finally, the display of age-specific death rates versus age, on the semilog plot, may often be nonlinear. As noted, leukemia mortality is characteristically phasic and therefore nonlinear. Other tumors, lesions, dose groups or genetic strains may also have nonlinear characteristics. Since we wish to estimate quantitatively the effects of lifetime irradiation, our approach is to derive the least-squares fitted polynomial equation that minimizes the variance. Measurements of excess risk, or mortality in excess of the control, can then be obtained, regardless of the form of the curves, by integrating the area between the control and experimental curves and reducing this value to terms of unit time [11,12]. This procedure will be discussed in more detail in a later section. The resulting measure of average displacement of the irradiated population from the control is expressed as the logarithm of the standard mortality ratio commonly used in epidemiology. This is the ratio of observed mortality to the mortality expected in a standard population, which in our case is the control. A conceptually similar procedure has been used by Ullrich et al. [20,21] to adjust age-specific incidence

data to the controls. The two procedures have not been concurrently evaluated for their consistency in deriving mortality ratios.

We have not yet developed standard errors for the estimated mortality ratios or displacements. Presumably they could be derived as a function of the errors of estimate associated with least-squares fitted age-specific mortality rate data. Standard errors that are given have been derived from variance analyses of the array of parameters developed for the dose by strain matrix.

RESULTS AND DISCUSSION

Mean After-Survival

One of the most consistent findings has been the observed exponential relationship between MAS and daily dose [4,15]. Table I presents the regression coefficients of the equation,

$$MAS_D = MAS_o e^{-\beta D} ,$$

for the two sexes and diverse strains and hybrids. Genetic variation is characterized by differences in the zero-dose intercept, not by variation in slope. The mouse can therefore be characterized by a common slope value of -0.037 per R/day or about -0.04/rad/day. This is equivalent to a loss of 4 days per 100 rads accumulated, which is one-fifth to one-tenth of the loss induced by single exposures [9,22].

If we assume that each species is characterized by its own life shortening coefficient that is independent of genetic variation, then one needs only this coefficient for man to predict his response to any low intensity continuous exposure to low-LET radiations. Can we derive an estimate from available data?

As data on the life-shortening effects of lifetime exposure of guinea pigs and dogs have shown [see 11,22], the life shortening coefficient per rad or roentgen increases as the species life expectancy increases. The increase over the mouse slope is roughly proportional to the ratio of life expectancies. If this holds for man, then the life-shortening coefficient for man should be approximately 30 times greater than that for the mouse. This estimate is based on a life expectancy for young U.S. adults at age 20 of about 20,000 days (55 years) [23]. While life expectancy for 100-day-old mice varies with strain (Table I), a figure of 1/30 of 20,000 or about 665 days is a reasonable value for the average mouse. The estimated life shortening coefficient for man is (30)(0.04) = 1.2 days/rad/day or 1.2 days per rad accumulated at the lowest intensities.

A note of caution is required. Although the data from the guinea pig and dog experiments generally support the above argument, there is no way to confirm the assumption directly for man. Sacher [13] cautions that, while the practice of species equalization by a transformation of the age scale has theoretical and experimental credibility, the procedure might be incorrect because the factor of 30 may not fully account for species differences in the intercept of the mortality rate slope. This method of transforming the age scale does need further evaluation. In the interim, we offer the life

shortening coefficient of 1.2 days/rad, based on the approximate 30-fold ratio of MAS values from young adulthood, as one extrapolation to man.

Age-Specific Mortality Rate

Following single exposures, the death rate slope remains generally parallel to the control but is displaced upward [8,9,12]. Excess mortality is therefore easily defined by the displacement of the intercept of the regression of age-specific mortality rate on age (the Gompertz displacement defined by Sacher [8,9]). This displacement can be used to estimate the life shortening coefficient in days per rad for mice (~ 26 to 44 d/R [9]), to compare species, and to render extrapolations to man or other animals [9]. These general procedures and their application need no further elaboration for the case of single exposures, but they have not been fully explored for continuous exposures given over the adult life, although there is ample documentation that the effect of continuous exposure is manifest as a progressive divergence of the age-specific death rates from the control as age increases and dose accumulates [8,9,11,12].

For the sake of brevity, we will confine our analysis to the comparison of inbred strains A/J, BALB/c, and C57BL/6, and the $B6CF_1$ hybrid. Data from the two sexes are combined. This does not introduce a bias, because they follow parallel responses, with the female generally showing higher incidences of tumors and slightly steeper regressions of mortality rate on age. The analysis is also restricted to exposures of 0, 1.3, 2.6, 6, 12, 24 and 32 R per day, starting at 100 days of age and continuing for the duration of life. The age-specific mortality rates were fitted with first or second degree polynomial equations through a common 100-day intercept for all exposure groups within each strain. The data are presented in three ways:

1) deaths from all causes;

2) deaths with one or more tumors;

3) deaths without evidence of a tumor.

The mean after-survivals and other pertinent results are given in Tables II and III.

The area between slopes, control versus experimental, as previously noted, is used to develop expressions of excess risk in terms of the mortality ratio. For derivations involving nonlinear equations, the area between the two curves, taken to the age interval of last death for the irradiated cohort and divided by the number of days between that age and 100 days, provides an estimate of the natural logarithm of the average lifetime mortality ratio, or ln MR, for the specified daily exposure rate. The antilog gives the average lifetime ratio of observed over expected mortality or the factor of increase in death rate for that exposure cohort.

If the cumulative area is sequentially derived and divided by the number of days over which the area or displacement is calculated, a measure of ln MR is derived that is related to accumulating exposure in roentgens (or rads). Thus, one can calculate the coefficient of fractional increase in mortality ratio per roentgen, which, in turn, can be related to the reduction of life expectancy. This procedure can estimate the average life shortening coefficient for the specified cause of death. It is directly comparable to life shortening coefficients derived by Sacher from the Gompertz equations

describing the response of mouse, rat, guinea pig, and dog populations subjected to single exposures [9].

When all compared mortality-rate slopes are linear, the derivation reduces to manipulations of the increment of increase (or decrease) in slope. Thus:

$$\ln MR = [(k_D - k_0)]\Delta t/2 ,$$

where k_D and k_0 are the Gompertz slopes for the irradiated and the control (fitted through a common intercept) and Δt is the lifespan (days from start of exposure to last death) of the irradiated group. The increase in average ln MR per R accumulated is:

$$\ln MR/R = \left[\frac{(k_D - k_0)/2}{R/day}\right].$$

A close relationship obviously must exist between the mortality ratio and the average life shortening (LS), so that

$$LS = z \ln MR ,$$

where z is the number of days lost per log cycle increase in the mortality ratio. The experimentally-derived value of z is between 140 and 170 days. A theoretical expectation of 164 days was given in a previous report (11). The product of (z)(ln MR/R) provides a life shortening coefficient in terms of days/R. Figure 1 presents an example of the fitted mortality-rate data for the $B6CF_1$ hybrid used to derive the mortality ratios.

All Causes of Death

The regression coefficients of ln MR/R in Table III reveal little variation among the average slopes for the four exposure levels between 1.3 R/day and 12 R/day. According to a variance analysis, significant variation does exist among strains, but not among the four doses. If we include the data from 24 R/day in the analysis, then variation among the dose rate groups rises to the 5% level of statistical significance. Thus, we conclude that daily low intensity external γ-irradiation at 12 R/day and below induces excess mortality at a rate that depends only upon accumulated dose, and that is independent of daily or hourly exposure rate. The average slope is 0.19 ± 0.01 ($\times 10^{-3}$) per roentgen or 0.21×10^{-3} per rad. There is not much variation among the strains except for A/J which shows little radiation-induced excess mortality at these low-level exposures. This strain is characterized by a high incidence of death from chronic liver and kidney degeneration, an amyloid infiltration disease, that swamps the effects of low levels of radiation injury. The strain is included in this analysis, since it may represent a genetic variant of any mammalian population, including man.

Up to 12 R/day, life shortening from all causes of death averages 0.031 days per roentgen for these four dose rates and genetic groups, ranging between 0.011 to 0.045 days/R among strains, and between 0.022 and 0.036 among dose rates. Above 12 R/day, the life shortening coefficient begins to rise rapidly, and the variance becomes more dependent upon dose rate than upon genetic factors.

All Deaths with Tumor

Since more than 50% of the mice die with evidence of one or more tumors (Table II), excess risk from tumor-related death closely matches that

described for the category of all causes (Table III). The mortality ratios are greater, and the regressions of ln MR on accumulating exposure are steeper.

The variation among the four lowest exposure groups is not statistically significant and the average slope of ln MR on accumulating exposure is 0.25 ± 0.04 ($\times 10^{-3}$)/R (Table III). Again, the A/J strain diverges most from its peers. At the highest exposures of 24 and 32 R/day, the $B6CF_1$ and one of its parents, the C57BL/6 strain, reveal a somewhat higher than average rate of increase in excess mortality with tumors. This is due to sharp increases in the induction of reticular tissue tumors (leukemias) in these two strains.

One important finding emerges. Although sampling is limited, there is no significant correlation between the spontaneous incidence or rate of tumor mortality and the induced tumor mortality ratio per R. The induced rate per R per day is variable, however, and is positively correlated with the spontaneous rate. If the induced rate per R had been invariant, the mortality ratio would have been negatively correlated with spontaneous rate. In other words, the mortality ratio, or relative risk, is the less variable measure of determining excess tumor risk from low levels of radiation. Excess mortality with tumors occurs in a more nearly constant ratio to the spontaneous rate, rather than as a constant rate per rad per mouse-day.

An example may serve to clarify this observation. Table IV compares the two parent strains, BALB/c and C57BL/6, and their F_1, all of which have a generally uncomplicated response to radiation (as compared to strain A/J), at 0 R/day versus 12 R/day, and at the single time of 400 days after initiation of exposure. The log mortality ratio is nearly constant, but the increment of excess deaths varies from near 900 to over 4000 per million mice per day. The rate per total accumulated exposure ranges from 19 to 87 ($\times 10^{-8}$) per R, with the F_1 intermediate between the two parents. The percentage increase per R only varies by a factor of two, and the hybrid has the highest rate of increase over its control. Although this limited comparison cannot settle the argument concerning the appropriateness of either relative risk or absolute risk for environmental impact assessment [3], it does add strength to the position that the relative risk assumption may be more correct for the usually uncharacterized and heterogeneous human population.

Deaths without Tumor

The mortality ratios in this residual category show a surprising degree of similarity among all four strains at the two highest exposure levels (Table III), although the incidence of nontumor deaths ranges between 30% and 90%. This may reflect the emerging importance of hematopoietic system injury at these highest exposures. In comparison, at the lower exposure levels, where nontumor deaths range more narrowly between 25% and 65% among the strains and doses, the data are extremely variable and no single source of variation is significant. The average rate of increase in ln MR/R is low, 0.09×10^{-3}/R, for all strains at 1.3-12 R/day. Since an average of 40% of the mortality is assigned to this category at these doses, the weighted contribution of nontumor deaths to the mortality ratio is $(.4)(.09 \times 10^{-3}) = .036 \times 10^{-3}$, as compared to those deaths with tumors, $(.6)(.25 \times 10^{-3}) = .15 \times 10^{-3}$. The sum, 0.186×10^{-3}, approximates the observed value for all causes, 0.19×10^{-3}. Thus, about 80% (0.150/0.186) of the

life shortening is due to excess mortality related to the occurrence of neoplastic disease. These observations quantitate our previous suggestion [12] that most or all of the excess risk at 6 R/day and below was due to tumor-related mortality. This is also consistent with other information from the study of irradiated animals and man [24,25].

Extrapolation to Man

There are no secret solutions to this problem. Any one of the mouse-based coefficients of injury regardless of dimensions, can be translated to human equivalence. The underlying assumption is that the mortality rate slopes (Gompertz slopes) for mouse and man are in an inverse ratio of radiosensitivities. This is the approximately 30:1 mouse:man ratio noted earlier in this discussion. In addition, there is the assumption that the ratio of slopes, or the slope displacement, has an identical relationship to the reduction of life expectancy in both species, as postulated by Grahn [11]. A number of relationships between the Gompertz slope, the mortality ratio, and the life expectancy have been and can be demonstrated. Among these, the ratios MAS_D/MAS_0 and k_D/k_0 are seen to be highly correlated, in terms of a power function, for all the separate strains and hybrids, which leads to our assumption that the slope displacement or mortality ratio is related to the fraction of life lost independently of species differences in life expectation.

In the present data, $\left[\frac{MAS_D}{MAS_0}\right] = \left[\frac{MR_D}{MR_0}\right]^{-.42} = (MR)^{-.42}$, since MR_0 always equals 1.0. The power function coefficient of -0.42 ± 0.01 is the common value among the four genetically different groups. Since the regression of ln MR on dose averages 0.00019 (Table III), that is, $MR_D/MR_0 = e^{0.00019D}$, it follows that the fraction of life lost per unit dose by the average mouse is equal to $1 - (MAS_D/MAS_0) = 1 - (MR)^{-.42} = 1 - (e^{0.00019D})^{-.42}$. The latter reduces to $(1 - e^{-8\times10^{-5}D})$ per R, or $(1 - e^{-9\times10^{-5}D})$ per rad. This is approximately the same as the α term of 65×10^{-6}/R, given by Sacher [26] as the low dose-rate dose-effect constant for mice that was derived by a somewhat different approach [27,28].

A total dose of 250 rads delivered over the lifetime would produce 2.22% life shortening according to the data given here. This is 15 days for the average 100-day-old mouse and 445 days for the average 20-year-old human. Life shortening for man would amount to about 1.8 days per rad, which is slightly greater than the figure of 1.2 days derived on the basis of the relation between MAS and the daily exposure level. The comparison of these values does not involve a truly independent pair of estimates, however, because the same data contribute to both. Different analytical pathways are used, though they eventually converge on the assumption that man:mouse extrapolation relies upon the ratio of life table constants.

Finally, the above example suggests that a total lifetime dose equal to the present maximum permissible dose of 5 rem per year for 50 years of occupational exposure, delivered at the rate of about 100 mrem per week, would induce a 15-month reduction in life expectancy.

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TABLE I. COEFFICIENTS FOR THE REGRESSION OF ln MEAN AFTER-SURVIVAL (MAS) ON EXPOSURE IN R PER DAY.

STRAIN OR HYBRID	SEX	EXPERIMENT 1 CONTROL MAS ± SE (DAYS)	EXPERIMENT 1 β ± SE (FRACTION LOST PER R/DAY)	EXPERIMENT 2 CONTROL MAS ± SE (DAYS)	EXPERIMENT 2 β ± SE (FRACTION LOST PER R/DAY)
A/J	♂	458 ± 20	-0.038 ± .002	502 ± 12	-0.036 ± .002
	♀	487 ± 20	-0.038 ± .002		
BALB/c	♂	387 ± 21	-0.040 ± .001	609 ± 14	-0.042 ± .001
	♀	453 ± 19	-0.041 ± .002		
C3Hf/He	♂	399 ± 22	-0.035 ± .001		
	♀	423 ± 21	-0.036 ± .002		
C57BL/6	♂	576 ± 26	-0.038 ± .002	645 ± 14	-0.038 ± .001
	♀	584 ± 21	-0.038 ± .001		
C57L	♂			534 ± 10	-0.028 ± .001
	♀				
$B6CF_1$	♂	759 ± 26	-0.033 ± .001	753 ± 10	-0.037 ± .001
	♀	782 ± 26	-0.033 ± .001		
$B6CF_2$	♂	548 ± 27	-0.036 ± .001		
	♀	561 ± 24	-0.037 ± .001		
Mean: (per R/day)			-0.037		-0.036
(per rad/day)			-0.04		

TABLE II. BASIC STATISTICS FOR INDICATED MOUSE STRAINS AND EXPOSURE LEVELS. DATA FOR THE TWO SEXES COMBINED. REGRESSIONS OF ln AGE-SPECIFIC MORTALITY RATE ON AGE (k) GIVEN FOR ALL CAUSES OF DEATH FITTED WITH LEAST-SQUARES LINEAR EQUATIONS.

ITEM	EXPOSURE (R/DAY) 0	1.3	2.6	6	12	24	32	COMMON INTERCEPT (RATE/DAY)	CONTROL TUMOR INCIDENCE AT 800 DAYS (RATE/DAY)	(%)
A/J										
MAS[a] (days)	502	480	492	472	394	230	167			
Mort. ratio	1.0	1.12	1.11	1.18	1.89	5.42	11.5			
k ($\times 10^{-3}$/d)	7.20	7.51	7.52	7.74	9.62	19.50	31.63	1.2×10^{-4}		
No. mice	151	155	91	90	87	89	44			
% with tumors[b]	41.1	36.8	42.9	46.7	39.1	30.3	22.7	8×10^{-6}	129×10^{-4}	41.1
BALB/c										
MAS[a] (days)	609	567	509	499	382	230	162			
Mort. ratio	1.0	1.37	2.04	2.23	4.35	9.97	20.1			
k ($\times 10^{-3}$/d)	6.79	7.59	8.89	8.92	12.96	23.48	36.74	5.5×10^{-5}		
No. mice	151	150	81	89	81	91	44			
% with tumors[b]	57.0	62.7	56.8	67.4	63.0	27.5	11.4	15×10^{-6}	41×10^{-4}	45.0
C57BL/6										
MAS[a] (days)	645	602	573	580	476	263	194			
Mort. ratio	1.0	1.24	1.57	1.58	2.79	10.9	14.3			
k ($\times 10^{-3}$/d)	6.64	7.13	7.81	7.83	10.21	20.27	30.32	5×10^{-5}		
No. mice	135	141	81	83	88	91	41			
% with tumors[b]	31.1	44.0	35.8	37.3	40.9	58.2	41.5	9×10^{-6}	8×10^{-4}	21.5
B6CF$_1$										
MAS[a] (days)	753	705	677	590	457	291	210			
Mort. ratio	1.0	1.43	1.73	2.95	6.17	17.8	27.4			
k ($\times 10^{-3}$/d)	7.13	7.83	8.32	9.92	13.45	21.52	33.60	1.4×10^{-5}		
No. mice	303	301	181	182	89	87	44			
% with tumors[b]	62.7	78.4	76.8	74.7	62.9	52.9	65.9	5×10^{-6}	13×10^{-4}	32.7

[a]See ref. [11] for complete presentation of data by sex and strain.

[b]Percentage of all necropsied mice showing evidence of one or more tumors.

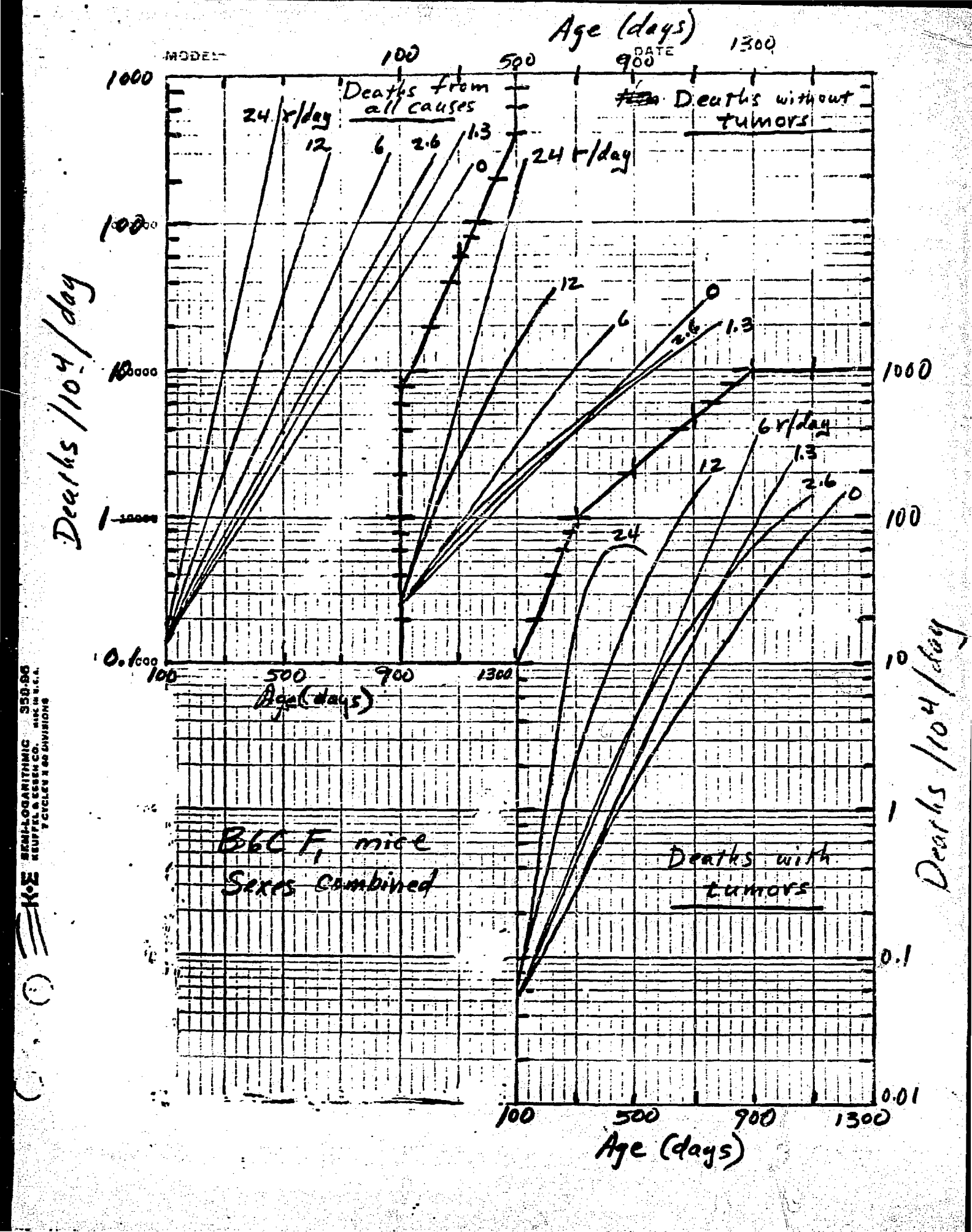
TABLE III. REGRESSIONS OF LOG MORTALITY RATIO (ln MR) ON ACCUMULATED DOSE (KILOROENTGENS) AND RELATED PARAMETERS. (See text for derivations and abbreviations.)

STRAIN	EXPOSURE LEVEL: (ROENTGENS/DAY) 1.3	2.6	6	12	MEAN 1.3-12	LS[a] (d/R)	24	LS (d/R)	32	LS (d/R)	z[a] (DAYS)
	Deaths from All Causes (ln MR/kiloroentgen)										
A/J	.11	.06	.04	.10	.079	.011	.26	.04	.38	.05	140 ± 8
BALB/c	.31	.40	.18	.26	.286	.045	.35	.06	.47	.07	157 ± 5
C57BL/6	.19	.22	.10	.15	.164	.027	.28	.05	.37	.06	166 ± 4
$B6CF_1$	.27	.23	.23	.26	.247	.041	.30	.05	.41	.07	167 ± 2
Mean ± SE	.22	.23	.14	.19	.194 ±.012		.30 ±.05		.41 ±.06		158 ± 6
LS (days/r)	.03	.04	.02	.03		.031		.047		.064	
	Deaths with Tumors (ln MR/kR)										
A/J	-.01	.05	.09	.16	.071		.37		.33		
BALB/c	.06	.40	.30	.26	.254		.27		.34		
C57BL/6	.69	.37	.17	.23	.364		.54		.49		
$B6CF_1$	.50	.23	.23	.24	.298		.39		.57		
Mean ± SE	.31	.26	.20	.22	.247 ± .043		.39 ± .05		.43 ± .06		
	Deaths without Tumors (ln MR/kR)										
A/J	.17	.07	.01	.09	.084		.24		.36		
BALB/c	-.09	.20	.01	.10	.056		.29		.40		
C57BL/6	.14	.21	.09	.11	.134		.20		.31		
$B6CF_1$	-.05	.02	.12	.24	.082		.24		.29		
Mean ± SE	.04	.13	.06	.13	.089 ± .025		.24 ± .02		.34 ± .02		

[a]Derived from equation; days of life shortening (LS) = z ln MR/R. See text for discussion.

TABLE IV. COMPARISON OF ABSOLUTE AND RELATIVE RISK ESTIMATES FOR DEATHS WITH ONE OR MORE TUMORS.

STRAIN	INTERCEPT AT 100 DAYS OF AGE	DEATH RATE PER DAY AT 500 DAYS OF AGE (400 DAYS OF EXP.)					
		0 R/d ($\times 10^{-6}$)	12 R/d ($\times 10^{-6}$)	EXCESS DEATH RATE: ($\times 10^{-6}$)	per R ($\times 10^{-8}$)	%/R	ln MR/R ($\times 10^{-3}$)
BALB/c	15×10^{-6}	373	4535	4162	87	0.23	0.26
C57BL/6	9×10^{-6}	117	1028	911	19	0.16	0.23
$B6CF_1$	5×10^{-6}	155	2599	2444	51	0.33	0.24


Age (days)
MODEL
DATE
100
500
900
1300
1000
100
10
1
0.1
Deaths /10⁴/day
Deaths from all causes
24 r/day
12
6
2.6
1.3
0
Deaths without tumors
24 r/day
12
6
2.6
1.3
0
6 r/day
12
1.3
2.6
0
24
B6C F₁ mice
Sexes combined
Deaths with tumors
Age (days)
Deaths /10⁴/day
1000
100
10
1
0.1
0.01
100
500
900
1300
Age (days)
K·E SEMI-LOGARITHMIC 359-96
KEUFFEL & ESSER CO. MADE IN U.S.A.
7 CYCLES X 90 DIVISIONS