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OSTEOSARCOMAS AMONG BEAGLES EXPOSED TO ^{239}PLUTONIUM

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ABSTRACT

A Weibull distribution was fit to the osteosarcoma death times of beagles given single intravenous injections of ^{239}Pu. For injected doses in the range 0-1 μCi/kg the osteosarcoma incidence rate h(t) at t days after injection can be fit by a quadratic function of injected dose d: $h(t) = 2.61 \cdot 10^{-18} d^2 t^{4.91}$. The best fitting linear function was rejected by the data ($p<0.001$). A different formula for h(t), derived from a multistage theory for osteosarcoma induction, was also fit to these data. For this purpose microdosimetry calculations were used to estimate the dose to the cells at risk in the endosteal layer (endosteal dose). According to the best fit, h(t) is a quadratic function of endosteal dose at low doses. A linear dose-response relationship was again rejected. The absence of a linear component at low doses might be explained by the fact that 108 of the 185 animals injected at the lowest doses (<0.02 μCi/kg) were still alive at the time these data were collected.

Key words: beagle osteosarcomas, maximum likelihood; multistage theory; plutonium; Weibull distribution.

INTRODUCTION

Man is exposed to the α emitter ^{239}Pu both occupationally, due to employment in the nuclear industry, and nonoccupationally, due to fallout from nuclear weapons testing. The 24000 year half-life of plutonium and its retention in bone, together with its toxicity in experimental animals, establish it unequivocally as a human hazard. However no cancers that are definitely attributable to ^{239}Pu have yet been reported in humans. Thus we must rely on experimental animals to infer the shape of the curve relating human bone sarcoma risk to plutonium dose.

Estimates of bone sarcoma risk in humans and animals corresponding to ^{239}Pu and ^{226}Ra are shown in Table I. The plutonium risk to humans of 200 bone sarcomas/10^6 person-rad of skeletal dose was obtained from bone sarcoma data on patients receiving repeated injections of 3.62-day ^{224}Ra. This is an α emitter which, like ^{239}Pu, decays to a large extent on bone surfaces.

The risk estimates in Table I are based on a linear dose-response model, the validity of which has been the subject of much recent discussion. Here we address this issue by examining the dose-response relationship for plutonium induced osteosarcomas in beagles, using data from the Radiobiology Laboratory at the University of Utah, kindly supplied to us by Charles Mays.

I. METHODS

As part of an ongoing study on the toxicity of plutonium, 243 young adult beagles were given single intravenous injections of monomeric ^{239}Pu (IV) in citrate solution, over the period from December 1, 1952 until October 17, 1974. An additional 51 animals served as controls. The distributions of age at injection and of injected dose for the animals considered in this report are shown in Figs. 1 and 2. The details of the experimental protocol have been described elsewhere (2). We are concerned here with the probability distribution

of time between ^{239}Pu injection and osteosarcoma occurrence. Osteosarcoma times are censored for animals who died from other causes, or who were alive on March 31, 1979, when these data were collected. A tabulation of animals by cause of death is presented in Table II.

II. RESPONSE VS. INJECTED DOSE

We first study the relationship between osteosarcoma risk and injected dose of ^{239}Pu in μCi/kg by fitting to the osteosarcoma times a Weibull distribution in which only the scale parameter depends upon dose. For this purpose the animals are grouped into the eight dose groups shown in Fig. 2, and the animals in each group are assigned the median dose for that group. Throughout this paper we assume that occurrence of censoring due to deaths from other causes or to study termination, and the occurrence of osteosarcoma, are two distinct processes that compete independently.

1. The Weibull Model

The Weibull distribution for the time T from ^{239}Pu injection until death from osteosarcoma, in the absence of other causes of death, is

$$F(t) = P(T<t) = 1 - \exp\{-\gamma(t-w)^k\}, \qquad t>w. \qquad [1a]$$

This distribution can also be described by the cumulative hazard

$$H(t) = -\ln\{1-F(t)\} = \gamma(t-w)^k, \qquad t>w, \qquad [1b]$$

or by the hazard or incidence rate

$$h(t) = \frac{dH(t)}{dt} = \gamma k(t-w)^{k-1}, \qquad t>w. \qquad [1c]$$

All three functions assume the value zero when $t<w$.

For empirical and theoretical reasons this Weibull distribution, with k and w independent of carcinogenic exposure and with γ dose dependent, has been applied extensively to cancer failure times (3-6). Empirically, it provides an adequate description of the power-of-age dependence of observed incidence rates

for many adult human and animal carcinomas. The theoretical justification for its use in chronic exposure experiments has been described by Pike (3). More speculative theoretical support for its use in this context derives from its occurrence as the consequence of a multistage theory of carcinogenesis associated with chronic exposures (7). According to this theory the parameter k is related to the number of stages through which normal cells progress to malignancy; w represents a fixed time period between malignant cell transformation and tumor detection, and γ depends on the rate constants for the progression.

We see from [1a] that the approximation $F(t) \simeq \gamma(t-w)^k$ holds for small values of risk $F(t)$. Thus at low doses the relationship between risk and dose is determined by the dose dependence of γ. We now examine the appropriateness of [1] for the beagle osteosarcoma data and present maximum likelihood estimates of the model parameters.

2. Parameter Estimation and Goodness-of-Fit

Figure 3 shows on a log-log scale the graph of empirical cumulative hazard $\hat{H}(t)$ for the six highest dose groups. The points $\hat{H}(t)$ were calculated as described by Nelson (8). The model [1] with $w=0$ predicts that these data points determine straight lines of constant slope k; thus Fig. 3 provides a visual check of its appropriateness. The points show no systematic deviation from parallel straight lines. Therefore we calculated maximum likelihood estimates for k, w and for the γ's corresponding to the eight dose groups. To do so we expressed the maximum likelihood estimates $\hat{\gamma}$ as functions of k, w and the data. Then the overall log-likelihood function to be maximized can be written as a function of k and w. This function is fairly constant over a wide range of pairs (k, w), making simultaneous estimation of k and w difficult, as is discussed in (4). Nevertheless we obtained the joint maximum likelihood estimates $\hat{k} = 4.33$ and $\hat{w} = 641$ days. The joint asymptotic 99% confidence region for k and w, and the

locus of points $\hat{k}(w)$, corresponding to fixed values w, are shown in Fig. 4. Exploratory analysis suggested that the shape of the curve relating the eight estimates $\hat{\gamma}$ to the median doses does not vary along the locus $\hat{k}(w)$. For this reason, and because w = 0 cannot be rejected by the data, we used the simple model w = 0 for all of the dose-response analyses of this section.

More rigorous checks of model validity than the visual check of Fig. 3 can be obtained by embedding [1] in a more general model and examining whether the ratio of the maximized likelihoods is significantly greater than unity. By applying this likelihood ratio criterion, we found that a more general Weibull model with w = 0 and with separate shape parameters k for each of the dose groups does not represent significant improvement (p=.34)[1]. Although it is not examined in this report, a likelihood ratio test of the Weibull model against a broad class of non-Weibull alternatives is also possible (9).

The straight lines in Fig. 3 correspond to the cumulative hazard [1b] with w = 0 and with maximum likelihood estimates of the remaining parameters given in part B of Table III. It is evident from Fig. 3 that at the two lowest doses shown the maximum likelihood estimates $\hat{\gamma}$ are less than estimates of γ one might obtain using the intercept of a line passing through the data points. This discrepancy is due to the large number of censored observations at the lowest doses and the loss of information on censoring times inherent in the graphical estimation procedure. For example, 108 of the 159 animals in the lowest dose group were censored before the first osteosarcoma occurred. Although the tumor-free time contributed by these 108 dogs reduces the maximum likelihood estimate $\hat{\gamma}$, it plays no role in determining the empirical cumulative hazard. Thus the intercepts of

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[1] In this test the controls were combined with the lowest dose group in order to have the two or more failures per group required to estimate the parameters of the more general model.

lines eye-fitted to the low dose data points tend to overestimate the corresponding parameters γ and distort the shape of the dose-response curve. Other implications of the extensive consoring at low doses are discussed in Section IV.

Also evident from Fig. 3 is the response reversal in the top two dose groups, a frequent occurrence in radiation carcinogenesis. This phenomenon is attributed to competition between radiation-related cell killing and the carcinogenic process.

Linear and quadratic functions relating the eight estimates $\hat{\gamma}_i$ to the median injected doses d_i were fit by different weighted least squares regressions. In all of these regressions, a pure quadratic function $\gamma(d)$ gave an acceptable fit, while a linear function was rejected. We will not describe the details of these analyses. Instead we present below an examination of the dose response relationship via likelihood ratio tests.

3. The Dose-Response Relationship

More restrictive Weibull models of the form $H(t;d) = \gamma(d)t^k$, with linear and quadratic constraints placed upon the function $\gamma(d)$, were fit to the data by maximum likelihood. In all model fitting each animal was assigned the median dose for its group, and a common shape parameter k was estimated. The models and fitted parameter values are shown in Table IV. To prevent the cell killing phenomenon from distorting the shape of the dose-response curves, the γ parameter for the highest dose group was not required to satisfy the constraint on $\gamma(d)$.

This data set contains the only spontaneous osteosarcoma death ever experimentally observed. To assess the effect of this anomaly on our results, the analyses were carried out both excluding and including the control animals.

Using the reduction in maximized log-likelihood as criterion for goodness-of-fit, models 2 and 3 of Table IV were compared with model 1. The χ^2 statistics obtained in these comparisons, and their p values, are shown in the last column of the Table. From these values it is evident that the quadratic models provide

acceptable fits to the data for doses less than one μCi/kg, and that the linear dose-response relationships specified by models 2 must be rejected. Models containing both a linear and a quadratic component for $\gamma(d)$ did not fit the data significantly better than did models 3. Moreover the linear component in those models was negative.

We see from Table IV that the dose-response relationship is not sensitive to the anomalous osteosarcoma among the controls. Indeed, even the quadratic coefficients in models 3A and 3B are very similar. However the spontaneous incidence rate is undoubtedly overestimated by model 3B. Changing units from kilodays to days, we find that the cumulative hazard of 3A, for dogs injected with d μCi/kg at t days after injection, is

$$H(t;d) = 4.31 \cdot 10^{-19} d^2 t^{5.91}. \qquad [2]$$

In the Discussion we shall compare the low dose risk predicted by [2] with the linear risk estimated for ^{239}Pu shown in Table I.

III. RESPONSE VS. ENDOSTEAL DOSE

The analysis of the previous section suffers from two defects. First, each animal was assigned a median dose rather than its actual injected dose. Second, injected dose is a less meaningful index of carcinogenic exposure than is endosteal dose rate, i.e. the dose rate to the endosteal cells lining the bone surfaces. In this section we avoid these defects by estimating the endosteal dose rate for each animal under study. We then use these estimates to fit to the data a multistage theory for the induction of osteosarcomas by ^{239}Pu that includes a competitive, dose related cell killing effect. We first describe the theory, which generalizes that of Marshall and Groer (10) for osteosarcomas induced by ^{226}Ra in beagles and by ^{226}Ra and ^{228}Ra in man. Next we calculate the endosteal dose rate as a function of injected dose and of time since injection. Using these calculated dose rates we estimate the parameters in the theory by maximum likelihood. Then we examine the goodness of fit of the theory and its

implications for the relationship between osteosarcoma risk and endosteal dose.

1. The Theory

The theory assumes that endosteal stem cells near the bone surface are transformed to malignancy in three stages. The first and second transitional events occur sequentially at rates proportional to the endosteal dose rate, with common proportionality factor ρ. A fraction π of all first events takes a normal cell directly into stage two. This would be the case if transformation involved two targets in the cell nucleus, both of which were hit by some of the α particles passing through the nucleus. Transition to the third (malignant) stage is not related to radiation, but occurs at a rate proportional to a power β of time since injection, with proportionality factor λ.

A schematic diagram of the process is shown in Fig. 5. Cells in stages one and two are at high risk of radiation-related death, which occurs with probability $\kappa c(t)$, where $c(t)$ is the endosteal dose rate. All endosteal stem cells are assumed to be normal at the time of injection. The rare spontaneous beagle osteosarcomas are neglected. The special case $\pi=\beta=0$ yields Marshall and Groer's theory.

The hazard rate predicted by the above theory is approximately

$$h(t) = \xi(1-e^{-\kappa D}\{1+(\kappa-\phi)D\})(t-w)^{\beta}, \qquad t>w. \qquad [3]$$

Here $\xi = N\rho^2\lambda(1-\pi)/\kappa^2$, N is the number of endosteal cells at risk, $\phi = \pi\kappa^2/(1-\pi)\rho$, and D is the total endosteal dose in rads at $t-w$ days after injection. As usual, the hazard rate is zero for $t<w$. The approximation [3] is valid provided each of the three transition rates, integrated over the animal's lifetime, is small relative to unity. However the killing constant κ need not be small. The derivation of [3] can be found in (7) as a special case of a general multistage theory of carcinogenesis. In the following analysis the growth time w will be preassigned and the four parameters ξ, ϕ, κ and β will

be estimated by maximum likelihood. Note that the distribution [3] is not Weibull because the factor corresponding to γ depends upon time through the total dose D.

At low total doses we have the further approximation

$$h(t) \simeq \{\xi\phi D + \xi\kappa(\kappa-\phi)D^2\}(t-w)^{\beta}.$$

Here and throughout the remainder of this section t is taken greater than w. Note that at low doses the relationship between hazard rate and endosteal dose has both a linear and a quadratic component, provided that $0<\pi<1$. When $\pi = 0$, so that transition of normal cells directly to stage two is impossible, then $\phi = 0$ and we see from [3] that

$$h(t) = \xi\{1-e^{-\kappa D}(1 + \kappa D)\}(t-w)^{\beta}, \qquad [4]$$

which at low doses becomes approximately quadratic in dose:

$$h(t) \simeq \xi\kappa^2 D^2(t-w)^{\beta}. \qquad [5]$$

On the other hand when $\pi = 1$, so that transformation is a two stage process with one radiation related event, we find from [3] that

$$h(t) = \xi\phi De^{-\kappa D}(t-w)^{\beta}.$$

In this case we have at low doses

$$h(t) \simeq \xi\phi(D-\kappa D^2)(t-w)^{\beta},$$

so that the curve relating hazard rate to dose begins linearly at zero dose and becomes concave downward as dose increases.

2. The Endosteal Dose Rate

To estimate the dose rate $c(t)$ to endosteal cells within 0-10 μm from bone surface at t days after injection, we assume that the total bone weight of a young adult beagle comprises 3.75 percent of its total body weight at injection (1). Thus one μCi of ^{239}Pu per kilogram body weight yields

$$\frac{1\ \mu Ci}{kg\ body\ wt.} \cdot \frac{1\ kg\ body\ wt}{.0375\ bone\ wt} = 26.6\ \mu Ci/kg\ bone\ weight.$$

Now 26.6 μCi of plutonium in one kilogram of bone yields an average skeletal dose rate of

$$(26.6\ \mu Ci/kg)\cdot(0.268\ \text{rad/day per}\ \mu Ci/kg) = 7.14\ \text{rad/day},$$

where the conversion factor 0.268 rad/day per μCi/kg was obtained from Mays (personal communication).

However not all of the plutonium initially deposited on the bone surface remains there. Some of it is eliminated or deposited in the liver, and some is buried under the apposition of new bone mineral. According to the calculations of Stover (11), the fraction of ^{239}Pu retained within the skeleton at t days after injection is given by $pe^{-.0011t} + (.5 - p)$, where p depends upon the dose injected as shown in Table V. Thus the average dose rate to the skeleton at t days after the injection of 1 μCi/kg in a young adult animal is

$$7.14\ \{pe^{-.0011t} + (.5 - p)\}\ \text{rad/day}. \qquad [6]$$

Marshall et al. (12) estimate the ratio of endosteal dose rate to skeletal dose rate to be 12.8 for a surface source of ^{239}Pu and 0.43 for a volume or interior source. Hence the ratio of endosteal dose rate to skeletal dose rate is a weighted average of these two ratios, weighted by the fraction of plutonium on the surface. The fraction of plutonium still on the surface of trabecular bone at t days after injection has been estimated by Marshall and Lloyd (13) as $e^{-t/365}$, the remainder being buried within the mineralized bone. Thus we take the ratio of endosteal dose rate to skeletal dose t days after injection to be the weighted average

$$12.8\ e^{-t/365} + 0.43(1-e^{-t/365}). \qquad [7]$$

Multiplying [7] by the skeletal dose rate [6] and the injected dose d yields the mean endosteal dose rate $c(t)$:

$$c(t) = 7.14d\ \{pe^{-.0011t} + (.5 - p)\}\ \{12.8e^{-t/365} + 0.43(1-e^{-t/365})\}\ \text{rad/day}. \qquad [8]$$

This assumes that all osteosarcomas arise from trabecular bone.

For a fixed choice of tumor growth period w, the total endosteal dose $D = \int_0^{t-w} c(x)dx$ at t-w days after injection was calculated from [8] for each of the 243 animals exposed to plutonium. Here t represents the time of osteosarcoma death or of censoring.

3. Paramater Estimation

The time w between malignant cell transformation and death was taken to be one year. This choice was based on the findings of Thurman et al. (14) on growth dynamics of beagle osteosarcomas. Table VI gives the corresponding maximum likelihood values of ξ, β, ϕ and κ. Details of the maximization are given in the appendix.

We see from the Table that the maximum likelihood estimate of ϕ is zero. Thus according to the maximum likelihood criterion, equations [4] and [5] give the best fitting hazard rate, one which is quadratic in dose at low endosteal doses.

The parameter estimates of Table VI are not directly comparable with those of Marshall and Groer for beagles exposed to ^{226}Ra. Unlike ^{239}Pu, ^{226}Ra is a bone volume seeker. This means that bone remodelling affects the endosteal dose rate less for this radionuclide than for ^{239}Pu. Thus Marshall and Groer took the conversion factor [7] relating skeletal dose rate to endosteal dose rate to be a constant, say C, independent of time. These investigators then estimated C, w and ξ from their data, while fixing $\kappa = 0.01$, and $\beta=\phi=0$. Their estimate of w is 2.5 years. When we fixed $w = 2.5$ and $\beta = 0$, we found our estimated cell killing probability $\hat{\kappa}$ to be significantly smaller than the value $\kappa = 0.01$ fixed by Marshall and Groer. Moreover this model ($w = 2.5$ years, $\beta = 0$) was rejected by the ^{239}Pu data according to the likelihood ratio criterion.

4. Goodness of Fit

In order to assess the goodness of fit of the multistage model to the data, the time from injection was divided into 16 intervals. For each interval the observed number of osteosarcoma deaths O was compared with the number E predicted by model [3] with the fitted values of Table VI. The results are displayed in Table VII. Also given in Table VII is a value of the chi-squared statistic testing overall goodness of fit for the 16 time periods. The table shows that the model cannot be rejected according to this criterion. A more detailed analysis, in which osteosarcoma deaths were partitioned according to injected dose and time, provided no further evidence of model inadequacy.

IV. DISCUSSION

The analyses of the last two sections show that at low doses the incidence rate of beagle osteosarcomas can be taken proportional to quadratic functions of both injected and endosteal dose, with no linear term in the functions. As might be expected, these results predict a substantially smaller plutonium induced osteosarcoma risk than that of 5200 bone sarcomas/10^6 beagles obtained in Table I from a linear model. We used the fitted Weibull model [2] to estimate the number of osteosarcomas expected after 12 years, in the absence of competing risks, among beagles injected with $0.12 \cdot 10^{-3}$ μCi/kg of ^{239}Pu. Here $0.12 \cdot 10^{-3}$ is the injected dose that yields an average skeletal dose of 1 rad in 12 years, as determined from the retention equations of Table V. Using the risk $F(t;d)$ specified by equations [1,2], we found that a million such animals would experience a cumulative risk of $10^6 F(12 \text{ yrs}; 0.12 \cdot 10^{-3} \mu\text{Ci/kg}) = 21.3$ osteosarcomas.

We also used the multistage model [3] with the parameter values of Table VI, together with the dosimetry equation [8], to predict the cumulative risk at twelve years experienced by 10^6 animals each injected at $0.12 \cdot 10^{-3}$ μCi/kg. We

found that 21.9 osteosarcomas are expected according to this model, in surprisingly close agreement with the Weibull prediction. The agreement lends support to both models. It also suggests that the more complicated multistage theory provides no further information about low dose risk than does the simple Weibull model [2].

The preceding estimate of 21-22 osteosarcomas contrasts sharply with the 5200 bone sarcomas predicted in Table I. The disparity emphasizes the difference between linear and quadratic predictions for low dose risk. It is thus important to ask what might explain the absence of a linear component for the present data.

One possible reason is the fact that the analyses did not include the occurrence of four deaths due to chondrosarcomas, which occurred at low injected doses (<0.05 μCi/kg). However a repetition of the above Weibull analyses with the four chondrosarcomas included as failures produced essentially the same results. Alternate analyses of these data that are based on the Cox proportional hazards model and that include the chondrosarcomas can be found in this volume (15). It is of interest to compare the results of (15) with those of the last two sections, not only to see the effect of including the chondrosarcomas, but also for the opportunity to compare estimates obtained using the Cox model with those of the present parametric models.

A second possible reason is the fact that while all of the animals injected at doses >0.02 μCi/kg were dead at the time these data were collected, 108 of the 185 animals injected at doses <0.02 μCi/kg were still alive then. (See Table II.) Hence subsequent osteosarcoma death among the animals injected at low doses might introduce a linear component which would dominate the dose-response curve at low doses, and narrow the gap between the preceding two risk estimates. Thus the ultimate outcome of this experiment, which should be evident within five to ten years, has important implications for the assessment of human risk from plutonium.

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APPENDIX

Let t_i denote the time that the i^{th} plutonium exposed animal fails (i.e. dies from osteosarcoma) or is censored, and let δ_i be an indicator assuming the value 1 if the animal fails and 0 otherwise. For a fixed choice of growth time w, the likelihood of the data for the plutonium exposed animals, conditional on the censoring times, is

$$L(\xi,\phi,\beta,\kappa) = \prod_{i=1}^{243} h_i(t_i)^{\delta_i} \exp\{-\int_0^{t_i} h_i(x)dx\}.$$

Here $h_i(\cdot)$ is the hazard rate for the i^{th} animal as specified by [3], with the animal's endosteal dose D estimated from the equation [8]. The logarithm of the likelihood function L was maximized by evaluation on a grid over the parameter space, combined with quadratic interpolation.

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TABLE I

Risk Estimates in Terms of Average Skeletal Dose Using Linear Model[a]

Nuclide	C57BL mice		Beagles	Humans
	Bone sarcomas		Bone sarcomas	Bone sarcomas
	10^6 mouse·rad		10^6 beagle·rad	10^6 person·rad
	male	female		
^{239}Pu	390	1200	5200	200[b]
^{226}Ra	77	70	320	6 to 53
RBE[c]	5	17	16	4 to 33

[a]Estimates taken from (1).

[b]Assuming ^{239}Pu risk = protracted ^{224}Ra risk.

[c]Relative biological effectiveness equals ratio of ^{239}Pu risk to ^{226}Ra risk.

TABLE II

Causes of Death for Dogs Injected with ^{239}Pu at Age 400 to 800 Days

Dose Range (μCi/kg)	Died from osteosarcoma	Died of other causes			Alive at end of study	Total
		Chondro-sarcoma	Other cancers	Nonmalignant causes		
0.00000	1	0	10	21	19	51
0.0005-0.0120	2	3	22	34	98	159
0.01390-0.01720	5	0	6	5	10	26
0.04310-0.04950	9	1	3	1	0	14
0.08460-0.11200	10	0	1	1	0	12
0.26100-0.31400	12	0	0	0	0	12
0.81100-1.03000	12	0	0	0	0	12
2.57000-3.17000	6	0	0	2	0	8
Total	57	4	42	64	127	294

TABLE III

Maximum Likelihood Estimates $\hat{\gamma}$ for Weibull Model $H(t) = \gamma t^k$, Where t is Kilodays since Injection

Median injected dose (μCi/kg)	A. Estimated without controls $\hat{k} = 6.37(0.46)$[a] $\hat{\gamma}$		B. Estimated with controls $\hat{k} = 6.49(0.46)$ $\hat{\gamma}$	
0	-	-	$1.60 \cdot 10^{-6}$	$(1.96 \cdot 10^{-6})$
0.0045	$2.67 \cdot 10^{-6}$	$(2.63 \cdot 10^{-6})$	$2.22 \cdot 10^{-6}$	$(2.19 \cdot 10^{-6})$
0.0158	$2.55 \cdot 10^{-5}$	$(2.13 \cdot 10^{-5})$	$2.11 \cdot 10^{-5}$	$(1.76 \cdot 10^{-5})$
0.0483	$2.44 \cdot 10^{-4}$	$(1.73 \cdot 10^{-4})$	$2.07 \cdot 10^{-4}$	$(1.46 \cdot 10^{-4})$
0.0959	$1.45 \cdot 10^{-3}$	$(8.49 \cdot 10^{-4})$	$1.26 \cdot 10^{-3}$	$(7.43 \cdot 10^{-4})$
0.2990	$3.24 \cdot 10^{-2}$	$(1.28 \cdot 10^{-2})$	$3.02 \cdot 10^{-2}$	$(1.19 \cdot 10^{-2})$
0.9070	$1.24 \cdot 10^{-1}$	$(4.22 \cdot 10^{-2})$	$1.18 \cdot 10^{-1}$	$(4.02 \cdot 10^{-2})$
2.7500	$4.17 \cdot 10^{-2}$	$(1.70 \cdot 10^{-2})$	$3.86 \cdot 10^{-2}$	$(1.58 \cdot 10^{-2})$

[a]Asymptotic standard errors in parentheses.

TABLE IV

Maximized Log-likelihoods and Parameter Estimates for Weibull Models $H(t;d) = \gamma(d)t^k$

where d is median injected dose and t is kilodays since injection

Controls	Model	Constraint[a] on $\gamma(d)$	Number of fitted parameters	$\hat{k}$	$\hat{\gamma}(d)$	Maximized log-likelihood	Likelihood[b] ratio test relative to Model 1
Excluded	1A	none	8	6.37	$\hat{\gamma}(0.0045)$ through $\hat{\gamma}(2.75)$ shown in Table IIIA	-43.47	-
	2A	cd	3	3.37	$0.252\ d$	-70.20	$\chi^2_5 = 53.46$ ($p<0.001$)
	3A	cd^2	3	5.91	$0.237\ d^2$	-46.83	$\chi^2_5 = 6.72$ ($p=0.25$)
Included	1B	none	9	6.49	$\hat{\gamma}(0)$ through $\hat{\gamma}(2.75)$ shown in Table IIIB	-46.74	-
	2B	$c_0 + c_1 d$	4	3.40	$6.42 \cdot 10^{-5} + 0.243\ d$	-75.61	$\chi^2_5 = 57.73$ ($p<0.001$)
	3B	$c_0 + c_1 d^2$	4	5.90	$2.65 \cdot 10^{-6} + 0.236\ d^2$	-50.52	$\chi^2_5 = 7.56$ ($p=0.19$)

[a]Constraint was not imposed on the parameter γ for the highest dose group.

[b]If model i is valid (i = 2,3) then twice the difference between maximized log-likelihoods for model 1 and model i is asymptotically distributed as a chi-squared variate on $\nu_1 - \nu_i$ degrees of freedom, where ν is the number of fitted parameters in the model.

TABLE V

Retention Equations for ^{239}Pu in Adult Beagles (Stover et al. (11))

Injected dose (μCi/kg)	≤0.1	0.3	1.0	≥3.0
Fraction of ^{239}Pu retained in skeleton at t days after injection	$.29e^{-.0011t} + .21$	$.15e^{-.0011t} + .35$	$.11e^{-.0011t} + .39$	$.07e^{-.0011t} + .43$

TABLE VI

Maximum Likelihood Estimates for Model

$$h(t) = \xi(1-e^{-\kappa D}\{1+(\kappa-\phi)D\})(t-w)^{\beta}$$

D represents accumulated endosteal dose in rads at t-w days after injection

Parameter	Description	Value
w	growth time	365.25 days (fixed a priori)
ϕ	dose-response determinant	0
κ	killing probability	$2.28 \cdot 10^{-4}$ rad^{-1}
β	"shape" parameter	3.10
ξ	"scale" parameter	$1.51 \cdot 10^{-9}$

TABLE VII

Observed Osteosarcomas vs Those Predicted by

$$h(t;D) = 1.51 \cdot 10^{-9}(1-e^{-2.28 \cdot 10^{-4}D}\{1+2.28 \cdot 10^{-4}D\})(t-365.25)^{3.10}$$

D is the total endosteal dose accumulated at t-365.25 days after injection

Interval (days)		Observed (O)	Expected (E)	$(O-E)^2/E$
0	365	0	0.00	0.00
365	731	0	0.18	0.18
731	1096	1	3.65	1.93
1096	1461	12	10.36	0.26
1461	1826	14	10.16	1.45
1826	2192	5	7.10	0.62
2192	2557	5	4.74	0.01
2557	2922	3	6.73	2.07
2922	3287	6	4.56	0.45
3287	3653	5	2.53	2.40
3653	4018	2	2.27	0.03
4018	4383	2	2.38	0.06
4383	4748	1	0.69	0.14
4748	5114	0	0.48	0.48
5114	5479	0	0.15	0.15
5479+		0	0.00	0.00
Total		56	56.00	10.24

$\chi^2_{12} = 10.24$ $\quad p = 0.59$

FIGURE LEGENDS

Figure 1. Stem and leaf display of age at injection in days for 294 dogs in the beagle ^{239}Pu study. Legend: 0057|41|88 represents two females injected at 410 days, one at 415 days, one at 417 days, and two males injected at 418 days.

Figure 2. Stem and leaf display of $\log_{10}$ injected dose in μCi/kg for 294 dogs in the beagle ^{239}Pu study. Legend: -32|996 represents two animals injected with $10^{-3.29}$ μCi/kg, one at $10^{-3.26}$μCi/kg.

Figure 3. Cumulative hazard for osteosarcomas in beagles vs time since injection of ^{239}Pu for the six highest dose groups at median injected doses in μCi/kg: 0.016 (■), 0.048 (□); 0.096 (●); 0.299 (○); 0.907 (△); 2.75 (▲). The data points were plotted by the method described by Nelson (8). Each point represents one osteosarcoma. The straight lines correspond to the Weibull cumulative hazard $H(t) = \hat{\gamma}_i t^{6.49}$, where the $\hat{\gamma}_i$ are given in part B of Table III.

Figure 4. Weibull log-likelihood surface for ^{239}Pu exposure data in which 57/294 beagle dogs developed osteosarcoma. The asymptotic 99% confidence region is outlined and the maximum likelihood values $\hat{k}(w)$ are plotted. The vertical line at 1066 days marks the first osteosarcoma time; the log-likelihood is negative infinity on the region to the right of this line.

Figure 5. Schematic diagram of multistage theory for induction of osteosarcomas by ^{239}Pu. Normal endosteal stem cells may progress to stage 1 at rate $(1-\pi)\rho c(t)$, or go directly to stage 2 at rate $\pi\rho c(t)$. Here $c(t)$ is endosteal dose rate of ^{239}Pu in rad/day at t days after injection. While transitions to stages 1 and 2 depend upon dose-rate, transition to stage 3 depends only on a power β of time since

FIGURE LEGENDS (continued)

injection, with proportionality factor λ. Partially transformed cells may be killed by the radiation at rate kc(t).

	33	8
	34	
	35	
	36	
	37	
	38	
	39	
7	40	66
0057	41	88
022249	42	6
	43	
	44	33335
222	45	2223
	46	
22	47	1299999
255555799	48	22444445555688999
00333444999	49	0133447777777899
0001133447789	50	000111123333444444566679999
023355666677779	51	23555556667777
01111122377799	52	011157999
00112233333336667888	53	0003333336667888
00225699	54	0022229999
122226	55	112
88999	56	06688
4	57	
9	58	5
4	59	68999
	60	22888
	61	
00	62	229
	63	0
122	64	2
008	65	17
	66	
	67	333
	68	
1	69	
	70	
	71	
	72	
9	73	
	74	
66	75	

Figure 1.

Injected dose (μCi/kg)	Osteo-sarcomas/ dogs injected	Median censoring time (days)	STEM-AND-LEAF DISPLAY OF COMMON LOGARITHM OF INJECTED DOSE	
(median dose)				
Controls	1/51	4080		00000000000000000000000000000000000000000000000000
.0005-.012 (.0045)	2/159	2922	-32	99644444433333320
			-31	7755420
			-30	
			-29	2211
			-28	43222
			-27	98777666666555555555555444443333 1000
			-26	98752
			-25	
			-24	764
			-23	5422110
			-22	99988888888777776666666666654320
			-21	99887
			-20	433322111100000
			-19	99998888888777766555543
.013-.017 (.0158)	5/26	3539	-18	665555522221000
			-17	99988887776
			-16	
			-15	
			-14	
.04-.06 (.0483)	9/14	2973	-13	74432222111111
			-12	
			-11	
.08-.12 (.0959)	10/12	1927	-10	77643221000
			-09	5
			-08	
			-07	
			-06	
.20-.30 (.2990)	12/12	-	-05	854433221110
			-04	
			-03	
			-02	
			-01	
.80-1.00 (.9070)	12/12	-	-00	98866533221
			00	1
			01	
			02	
			03	
2.5-3.0 (2.7500)	6/8	846	04	1334488
			05	0

Figure 2.

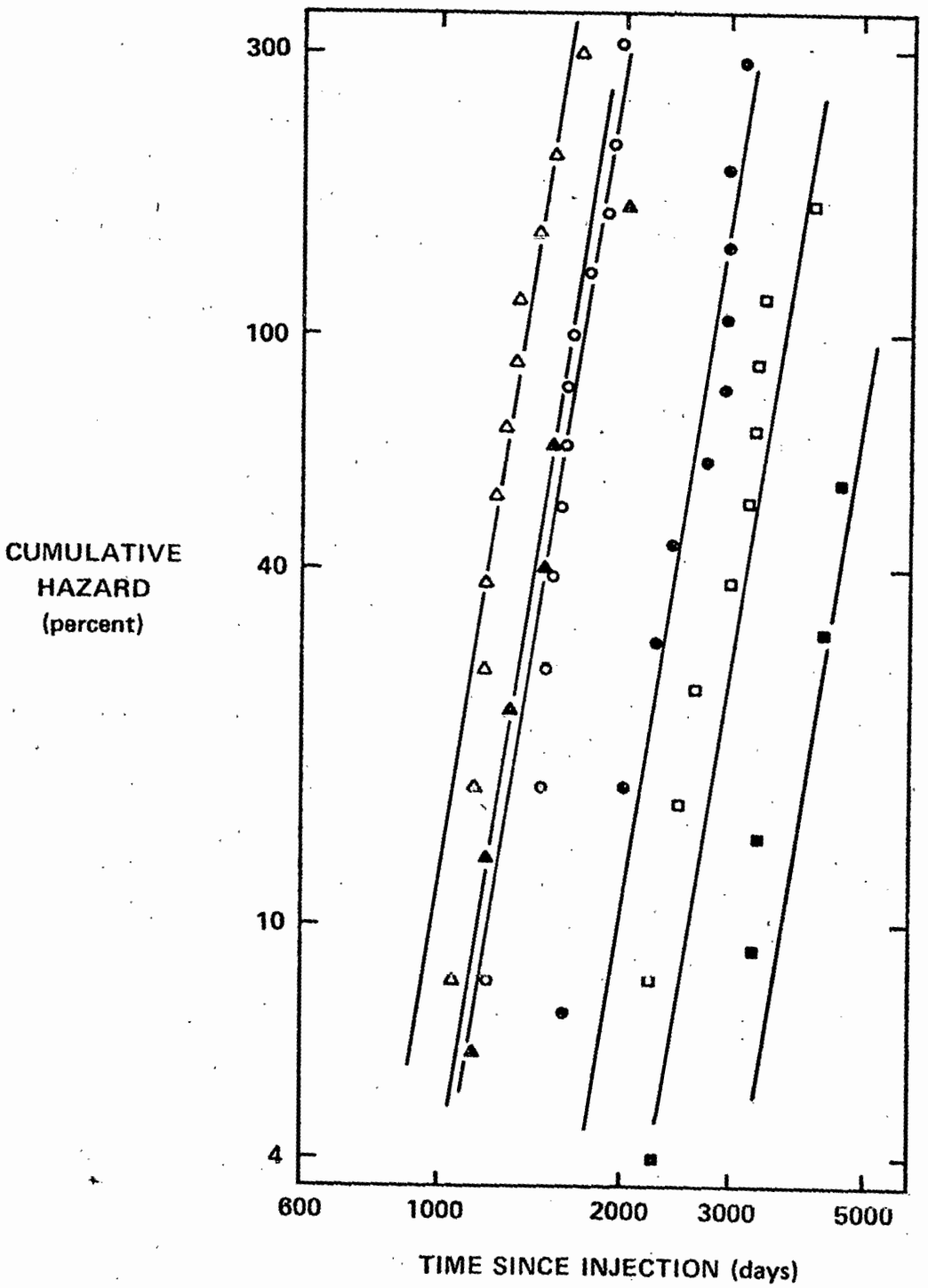
300
100
40
10
4
CUMULATIVE
HAZARD
(percent)
600
1000
2000
3000
5000
TIME SINCE INJECTION (days)

Figure 3.

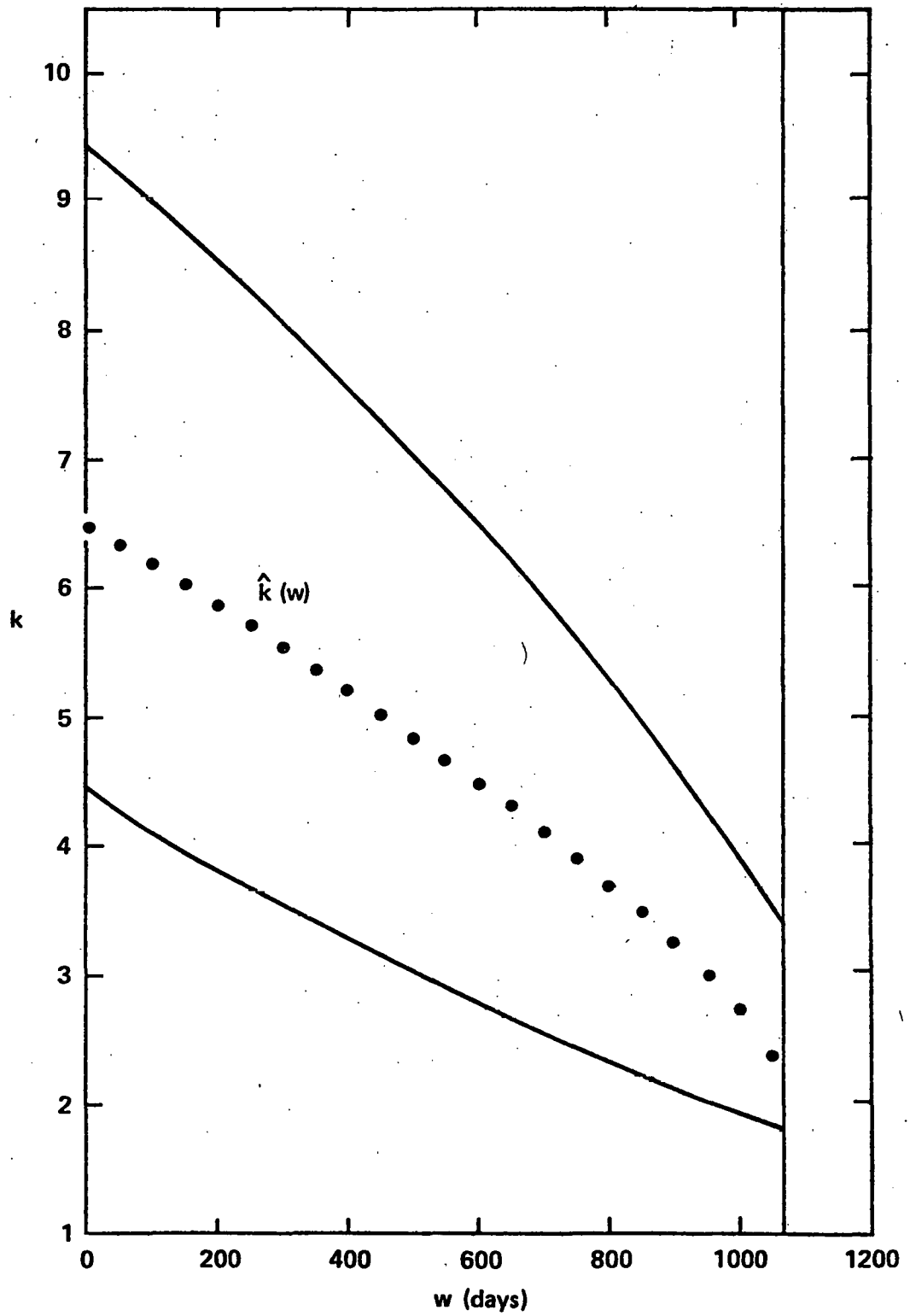

Figure 4.

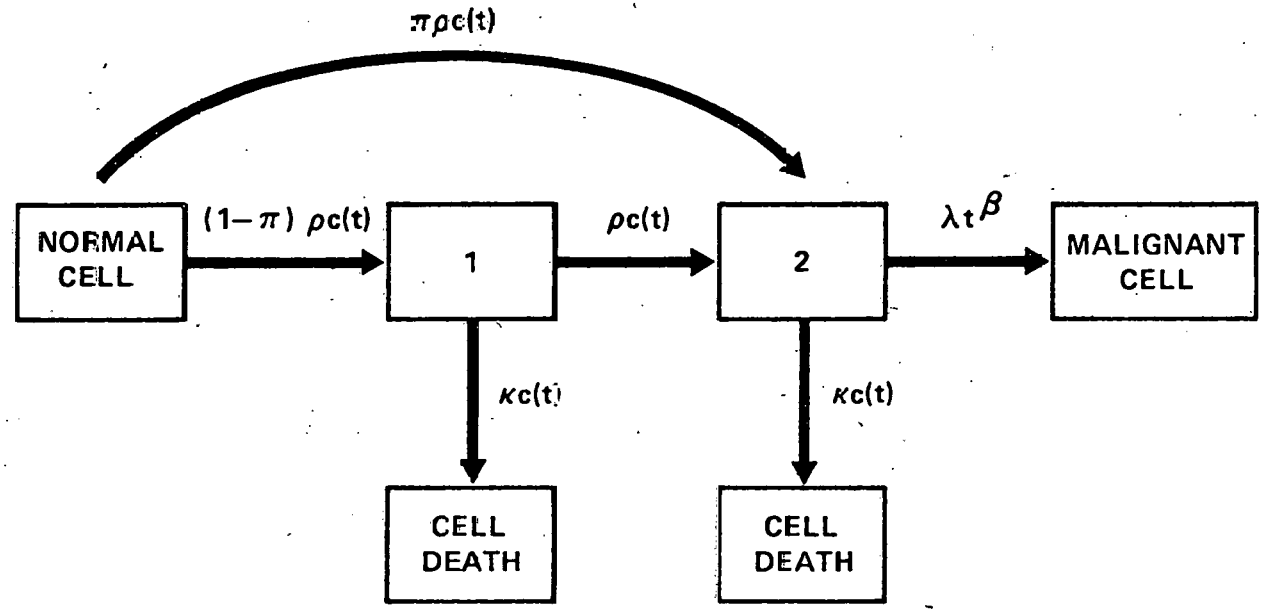
πρc(t)
NORMAL CELL
(1−π) ρc(t)
1
ρc(t)
2
λt^β
MALIGNANT CELL
κc(t)
κc(t)
CELL DEATH
CELL DEATH

Figure 5.