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Provisional Report: Radionuclides and PU Toxicity

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Provisional Report,: Grant # DE-FG03 98ER62674
Project # 55800112.

General:

The purpose of Grant # DE-FG03 98ER62674, Project # 55800112 was to continue a previously funded effort and make a statistical comparison of the respective toxicities of ^{226}Ra vs. ^{239}Pu in dogs. Special emphasis was on the induction of bone tumors that result from the alpha–radiation emitted from either radionuclide.With the support provided, we have completed the statistical analysis of ^{226}Ra and have established a sound basis for the analysis of the corresponding ^{239}Pu data and for the comparison of these 2 nuclides.
The analysis of the Ra project is the cornerstone for a determination of the Pu toxicity, as this will provide the link between animal experiments and existing human data.

Specifically:

Existing data obtained from the Ra project carried out at the University of Utah between 1952 and 1987 were reviewed. They are summarized in Table 1. For the present analysis , we selected nonparametric(1,2,3) and parametric procedures (4,5,6). The event time variable was either death from natural causes or death with bone tumor. It should be emphasized that all dogs diagnosed with bone tumor were euthanized when humanitarian reasons no longer justified keeping the animals alive. Throughout the project carried out at the University of Utah, surgical removal of bone tumors, as for instance by amputation of an affected limb, was not practiced, but soft tissue tumors were removed when possible. An analysis of failures from soft tissue tumors, especially mammary tumors and liver tumors, has been carried out and published previously (7-11). The Kaplan-Meier (12) (KM) weighted fractional survivals and the corresponding cumulative hazards for both modes of failure (death from all causes and from bone tumor) are shown in Figure 1.

The choice of a statistical model depends strongly on the statistical distribution of the data. Figure 2 shows that plots of (- ln cumulative hazard) vs. ln (t) approximate straight lines with slopes > 1. Coefficients of variation (r^2) for the respective slopes and intercepts all were in the range of 0.9 or greater, i. e. they are consistent with a Weibull distribution of the failure time variable (1). As in previous analyses, regression models with covariates were applied (4-6). The data can be applied to the accelerated failure time model and the proportional hazards model. In these models, the covariates act multiplicatively on the hazard function and additively on ln (t) (6). The proportionality condition was verified by showing that addition of a time dependent covariate produced a coefficient that was not significantly different from zero.

Covariates or confounders were chosen from an array of variables that, potentially, could modify survival. These covariates were used as linear and quadratic terms and in any combination that did not result in overstratification. In addition, dose level groups (GROUPS) which combine the effects of all confounders together were applied as categorical variables with and without specific confounders.

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The accelerated failure time model is decribed by (6):

$$Y = \alpha + z\beta + \sigma W$$

Where Y is the natural log of failure time, α is an intercept parameter, $z\beta$ is a vector of covariates and their coefficients, σ is a scale parameter whose reciprocal γ is the shape parameter and W is a variable with specified distribution, in this case the Weibull distribution. Thus, in addition to the estimation of the coefficients, the model requires the calculation of the intercept and the scale parameter. The exponentiated coefficients are a measure of the increase or decrease in hazard caused by a unit change in the covariate value. For the proportional hazards model, the estimated coefficients must be multiplied by the reciprocal of the scale parameter to yield a positive coefficient and an increment in hazard. For the accelerated failure time model, the estimated coefficients are negative if the covariate is associated with a decrease in life expectancy (or a decrease in survival time).

For each set of covariates and for each dosage level, the parameters calculated allow the construction of the needed survival and hazard curves and their comparison with the data derived from the KM analysis (12). The curves are based on the following relationships:

$$S(t)=\{\exp[-(\lambda t)^{\gamma}]\}^{\exp z_i\beta_i} \qquad h(t)=\lambda\gamma(\lambda t)^{\gamma-1} * \exp z_i\beta_i$$

(Survival) (Hazard)

in which λ is related to α in the model by: $\lambda = \exp(-\alpha)$ and the terms

$$S_0(t) = \exp[-(\lambda t)^{\gamma}] \quad \text{and} \quad h_0(t)=\lambda\gamma(\lambda t)^{\gamma-1}$$

are, respectively, the baseline survivals and baseline hazards, i. e. survivals or hazards in the absence of specified confounders. In many cases, this corresponds to the controls.

With all parameters calculated by the regression, failure times for the construction of survival curves were calculated as:

$$t = \frac{1}{\lambda}\left(\frac{-\ln(\text{Surv.Fraction})}{\exp z_i\beta_i}\right)^{\frac{1}{\gamma}}$$

with

$$\text{Median Surv. Time} = \frac{1}{\lambda}\left(\frac{\ln 2}{\exp z_i\beta_i}\right)^{\frac{1}{\gamma}}$$

Hazard curves based on : $h(t) = \gamma\lambda^{\gamma} * t^{\gamma-1}$ for each dosage level were calculated by performing the regression without specifying any covariates. These curves are shown in Figure 3, which also lists the exponential (instead of the power function) parameters and their coefficients of variation for each dosage level and for both modes of failure.

Exponentiated regression coefficients were used to calculate from the accelerated failure time model the change in life expectancy (life shortening) and using the proportional hazards model, the relative hazards with respect to the controls or with respect to an arbitrary reference. Selected survival curves and their underlying KM survivals are shown in Figures 4 and 5. The curves, from left to right, represent the survivals of the Ra40, Ra30, Ra20, Ra17, the collapsed dosage level groups and the Control group. Figure 4 exhibits the curves calculated without inclusion of GROUP as a covariate. None of the curves are in good agreement with the KM data, especially those with skeletal dose or dosesquare as covariates. Figure 5 shows the effect of including the categorical variable GROUP in the model. The fits are improved when compared to Figure 4. Curves with Rate, Ratesquare and GROUP, those with Rate* GROUP and Ratesquare and with GROUP alone gave the best fit. The dummy variables Rate* GROUP and Dose* GROUP were introduced to overcome numerical problems that arose during the calculation. Applying a Stepwise procedure (MPLR) (13) demonstrated that inclusion of additional covariates or use of other covariate combinations did not improve the model.

Table 2 lists survivals calculated by the regression. Median survivals and life expectancies can be compared with the original data shown in Table 1. Considering the small size of the individual groups, the calculated data do fit the actual KM data quite well. Also shown in Table 2 are the relative hazards with respect to a baseline hazard of the controls.

It was planned to apply the same statistical techniques to the bone tumor (BT) population, a cause specific failure, that were described above. Identical tests were performed to justify the application of these procedures, i. e. determination of the statistical distribution and verification of the proportional hazards condition. Cause specific failure time analyses are generally carried out by taking only those specific events (in this case bone tumors) as true failures and by censoring all other failures as loss to follow-up at the time of their deaths. However, for the present analysis, the number of true failures and their distribution within their respective dosage level subgroups required a somewhat unconventional approach. As shown in Table 3, there were a total of 31 bone tumors among 98 dogs. Among 62 beagles in the collapsed group (05-17), there were only 4 dogs with a bone tumor, and their deaths were not uniformly distributed over the survival curve. The estimated survivals of these four dogs fell between $S(t)=1$ and $S(t)=0.8$. A somewhat more favorable condition existed at dosage level =20 with 5 bone tumors among 13 dogs, of which only one had a survival $S(t)< 0.5$. The remaining 22 BT deaths occurred in the two highest dosage groups, level 30 and level 40. Listed are also the actual average number of days to failure with BT and the KM weighted Median days to failure, the average skeletal dose and dose rate. Considering that there was only one bone tumor among 120 control beagles, the choice of a suitable reference group appeared critical.

As for failures from all natural causes, KM-weighted fractional survivals were calculated for the bone tumor population. The corresponding graph in Figure 1 shows that the small number of tumors in the two low dosage levels together with the large number of dogs remaining at risk after the last BT dog had died, produced a skewed survival pattern. An identical picture is displayed by the respective cumulative hazards in the lower graph of

Figure 1. The BT events simply never reached the median survival time for the complete group. Nevertheless, as shown in Figure 2, plots of ln[-lnS(t)] vs. ln (t) could be described by straight lines of the form Y= a+bt and slopes > 1, and the coefficients of variation for the parameters were again close to 0.9. Inclusion in the string of tested confounders of a time dependent covariate produced coefficients that were not statistically different from zero. Therefore the proportionality conditions were not violated and application of the accelerated failure time and the proportional hazards, or relative risk, model were both justified.

Without specifying any covariates, survival hazards for each of the dosage level group of the BT population also were calculated as for failures from all causes:

$$h_0(t)=\lambda\gamma(\lambda t)^{\gamma-1}$$

The curves and the exponential forms of the calculated equations are depicted in the lower part of Figure 3. Coefficients of variation r^2 were 0.9 or greater. The graph emphasizes the sharp increase in hazard as the Ra dosage was increased to about 12 kBq/kg and higher.

Since neither the controls nor the low dosage level BT groups presented a suitable baseline hazard, different reference populations had to be used. Figure 6 shows five survival curves with different arbitrary baseline BT survivals. The top graph of Figure 6 shows the survivals obtained from using the Ra–injected dogs only and Ra 30 with 10/11 true failures as reference, i.e. Ra 30 = 0 and Ra 17 (05-17), Ra 20 and Ra 40 as covariates with value 1. Curves are from left to right for level 40, level 30, level 20 and level 17. The two center graphs include in the model the controls and the 4 Ra-injected groups. In the left graph, the actual deaths of the controls (Status=Status) are compared with each BT group (Status=BT). One has to consider that the natural lifespan of the controls represents the limiting age and also a relative risk of one. In the right graph the controls are again included in the model; however all but the single bone tumor were censored. Thus, controls and BT dogs were both given a (Status=BT) designation. The baseline BT survival calculated from

$$S_0(t) = \exp\left[-(\lambda t)^{\gamma}\right]$$

is included as the reference. The lower graphs again include the controls as well as the Ra-injected groups. In both cases the Status is BT. In addition to the GROUP covariates, cumulative skeletal dose (DSK) or average dose rate (RATE) are included as continuous variables, and the baseline survivals are given as a reference. All graphs correspond reasonably well to the respective KM survivals. The best fit was obtained for curves including average skeletal dose rate as a covariate while those with cumulative skeletal dose fit the least well. This was observed also with deaths from natural causes The effect of the low dosage level dogs remaining at risk after the last BT dog has died induced a numerical shift to survivals that are beyond the natural life expectancy. Numerical information on relative bone tumor risks and life expectancies for various models is shown in Tables 4 and 5. A summary of relative bone tumor risks obtained with various models used in the regression is found in Table 4. For convenience, the risk for the collapsed Ra 17 level was set arbitrarily to 1, and the corresponding risks of the other

groups were adjusted accordingly by adding or subtracting the calculated risk coefficients of the Ra group to the coefficients of the other groups. Depending on the model, BT risks defined as

$$\text{Risk} = \exp^{\Sigma(zi\beta i/-\sigma)}$$

vary widely, especially at the highest dosage level. Inclusion or omission of the master control group in the model either with a survival Status=1 or with BT=1 did not appear to lead to more consistent results. However, all models yield survival curves that conform reasonably well to the KM data. Keeping in mind the goal of this analysis (that is a comparison of the toxicities resulting from an internal burden of Ra or Pu, i. e. a toxicity ratio), it is not necessary to choose a specific model. If the analysis of Pu that is in progress at this time favors a certain model, that model can be used as long as the same one or the same baseline is applied to the Ra data also.
Life Expectancies calculated using the same models as for the Relative Risks in Table 4 produced median times to death with bone tumor observed at the two highest dosage levels that agree quite well with the Median KM survivals. The higher dosage levels are characterized by a high incidence of bone tumors and a low proportion of censored dogs. Thus, the events are uniformly distributed around the median of the whole population (true events plus censored dogs). The statistical power of these data, therefore, is high. For the low dosage groups, the number of censored dogs exceedes the number of events and the events are not uniformly distributed throughout the survival curve. Bone tumors fall mostly into the upper part of the curve where the fractional survival is high. The tumors, however, cannot be isolated from the whole population because we must include the nontumor dogs as long as these are at risk to develop a bone tumor. The model assumes that BT is the only mode of death. It disregards the fact that other modes of death will be in effect before BT can express itself. This leads to unrealistically long (hypothetical) median survivals that far exceed the normal life span of the dogs. The actual limiting life span then must be that of the control group. As pointed out above, this does not prevent us from using these results in our later comparison with the Pu population

The core of the Ra-Pu comparison now in progress will be the calculation of the respective hazard and survival information and the comparison with the actual KM data. Hazard ratios can then be calculated and relative risks of Ra /Pu for the two endpoints (failure due to all natural causes and failure due to bone tumor), will be determined

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TABLE 1

BASIC DATA FOR CONTROLS AND BEAGLES INJECTED WITH ^{226}Ra
(experimentally observed deaths from all natural causes)

(Dosage level) Inj.kBq of Ra /kg	# of Beagles /Group	# of Dead Dogs	# of Censored Dogs	KM - Weighted Av. Days Post Inj.	± σ	KM - Weighted Median[a]	Confidence Interval[b]	p - value[c]	Mantel Statistic
(02) 0.237	10	10	0	3991	219	3611	3448-4190	0.03	4.65
(05) 0.707	25	23	2	4434	117	4345	4180-4697	N.S.	0.92
(10) 2.116	23	18	5	4403	188	4065	3860-4557	N.S.	0.02
(17) 6.346	14	11	3	3984	293	3695	3254-4438	N.S.	1.58
(20) 12.728	13	12	1	3948	180	3775	3440-4368	<0.05	9.5
(30) 39.96	11	11	0	2211	137	2015	1897-2487	<0.001	163.3
(40) 119.88	12	12	0	1593	51	1553	1471-1614	<0.001	194
(Collapsed 05-10)	48	41	7	4428	105	4317	4141-4697	N.S.	
Controls	132	120	12	4432	76	4575	4234-4726		

a If no exact Median was obtained, the interpolated Medians were used.

b Brookmeyer-Crowley 95% confidence intervals for median survival time.

c p-value for the significance of difference from controls.
Level 17 was not statistically different from level 20, but level 20 was different from level 30 and level 30 was different from level 40.

TABLE 2

SURVIVALS CALCULATED BY PARAMETRIC REGRESSION [a]

Level	Median Days after Injection	± σ	Life Expectancy [b]	± σ	Relative Risk [b]	± σ
Collapsed (05-10)	4493	61	0.970	0.013	1.220	0.106
17	4186	161	0.922	0.022	1.719	0.297
20	3900	36	0.871	0.003	2.471	0.091
30	2282	47	0.480	0.024	127.8	42.08
40	1538	25	0.351	0.019	1180	191

[a] Average of 3 analyses with Group, Rate and Ratesquare as shown in Figure 5.

[b] Life Expectancy and Relative Risk of controls = 1.

TABLE 3

BASIC DATA ON THE OCCURRENCE OF BONE TUMORS

Parameters \ Dosage Level	05	10	17	05-17	20	30	40
# of dogs /group	25	23	14	62	13	11	12
Dogs with osteosarcoma	1	2	1	4	5	10	12
Avg.days to failure with BT (actual)				4264	3753	2275	1593
Median days to failure with BT KM-weighted				3644	4119	2099	1553
Avg. skel. dose at death –1 year(Gy)	0.8 ±0.12	1.66 ±0.77	3.57 ±1.69	1.744	8.95 ±1.98	19.1 ±4.03	43.3 ±15.1
Avg.dose rate to death – 1 year (mGy / day)	0.198	0.466	1.163	0.478	2.50	10.2	37.9

TABLE 4
SUMMARY OF RELATIVE BONE TUMOR RISKS CALCULATED FOR VARIOUS MODELS

Reference	Median (Days) for Reference	Ra 17[a]	Ra20[a]	Ra30[a]	Ra40[a]	Model
Ra 30=0	2356	1	11.9	1199	21820	Ra Dogs Only
Ra 20=0	4500	1	11.8	1199	21807	"
Ra 17=0	6367	1	11.8	1198	21823	"
Contr. vs. Each Group	4497	1	10.8	721.2	9191	Controls and Ra Dogs
Rate,Ratesqu. Groups [b]	8436	1	10.1	3245	46583	"
Dsk,Dsksqu. Groups [b]	8478	1	8.84	2544	77188	"
Groups	8848	1	12.2	1347	26662	Ra17= 02-17
Groups	8803	1	12.2	1349	26582	Ra17= 05-17
Each Group [c]		1	10.9	661.8	14030	Ra Dogs Only others excluded

[a] These Risks were calculated by considering only dogs with bone tumor as failures, others were censored. They assume that bone tumors are the only mode of death. Risks were arbitrarily based on the hazards of the respective Reference curves. They were then normalized to a risk of 1 for the collapsed low level group.

[b] Coefficients for Dose and Dosesquare were not significant; those for Rate and Ratesquare were significant.

[c] Individual Groups were compared against each other.

TABLE 5

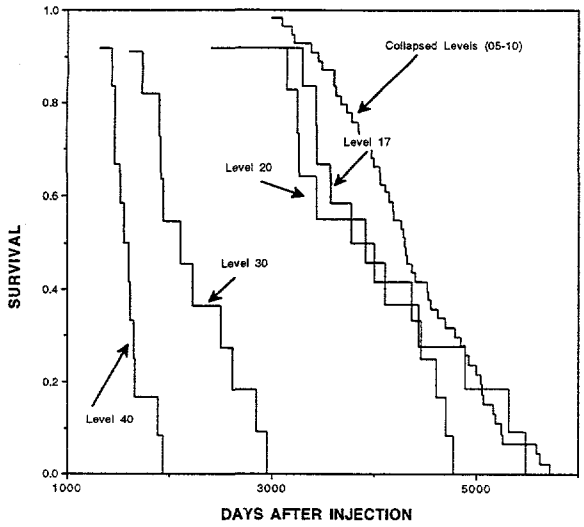
EFFECT OF Ra-DOSAGE ON LIFE EXPECTANCY CALCULATED FOR VARIOUS MODELS

Reference	Median (Days) for Reference	Ra 17 [a]	Ra20 [a]	Ra30 [a]	Ra40 [a]	Model
Ra 30=0	2356	6365	4498	2356	1568	Ra Dogs Only
Ra 20=0	4500	6367	4499	2357	1569	"
Ra 17=0	6367	6368	4500	2357	1566	"
Contr. vs. Each Group	4497	6581	4513	2318	1555	Controls and Ra Dogs
Rate, Ratesqu Groups [b]	8463	6016	4491	2174	1554	"
Dsk, Dsksqu. Groups [b]	8478	6433	4448	2394	1553	"
Groups	8848	6336	4497	2366	1573	Ra17= 02-17
Groups	8803	6389	4498	2364	1573	Ra17=05-17

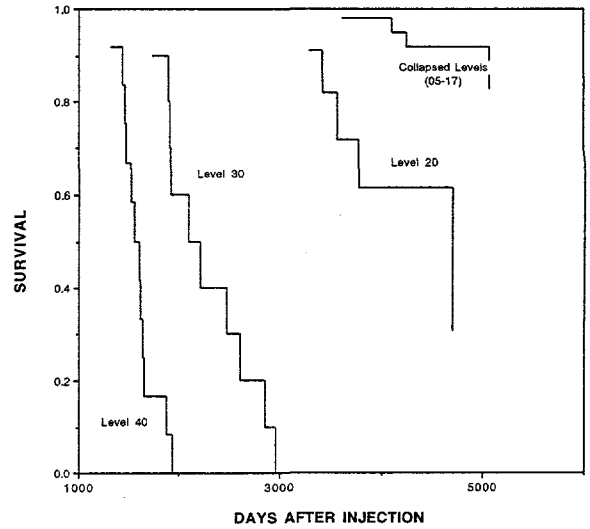
[a] These Median Days were calculated by considering only dogs with bone tumor as failures, others were censored. They assume that bone tumors are the only mode of death. In reality, days are limited to the life span of the control dogs. For Level 30 and 40, life spans are very close to those calculated for all deaths from natural causes

[b] Coefficients for Dose and Dosesquare were not significant, those for Rate and Ratesquare were significant.

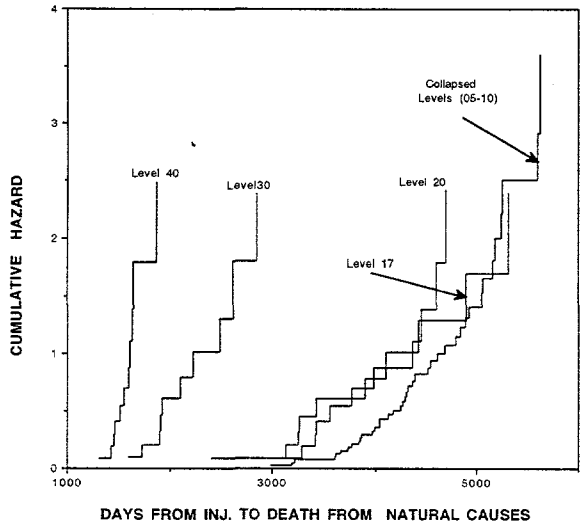
KAPLAN-MEIER WEIGHTED FRACTIONAL SURVIVAL
FAILURE IS DEATH FROM NATURAL CAUSES



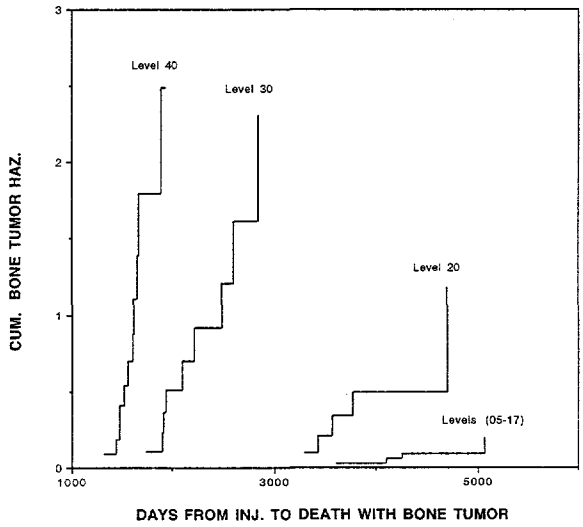
KAPLAN-MEIER WEIGHTED FRACTIONAL SURVIVAL
FAILURE IS DEATH WITH BONE TUMOR



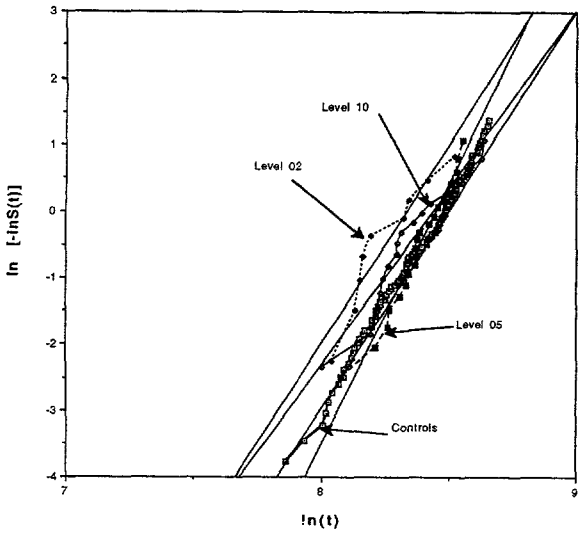
CUMULATIVE HAZARDS,
FAILURE IS DEATH BY NATURAL CAUSES



CUMULATIVE HAZARDS,
FAILURE IS DEATH WITH BONE TUMOR



TEST FOR STRAIGHT LINE
FAILURE IS DEATH FROM NATURAL CAUSES,
CONTROL AND LOW LEVELS (02 TO 10)



The plots of ln(-lnS(t)) vs ln(t) as represented by straight lines.The lines are described by the following equations and their r^2, all of which are in the 0.9 range.

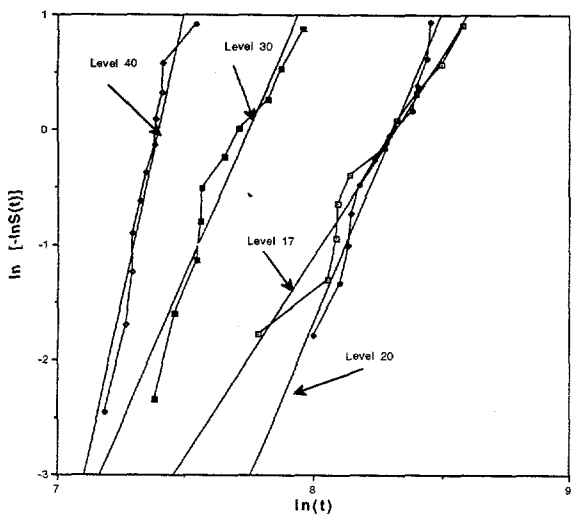
$y_{contr} = -53.085 + 6.2682\ x \quad (r^2 = 0.994)$

$y_{02} = -49.999 + 6.0006\ x \quad (r^2 = 0.899)$

$y_{05} = -66.466 + 7.8683\ x \quad (r^2 = 0.970)$

$y_{10} = -44.945 + 5.3287\ x \quad (r^2 = 0.936)$

DOSE LEVELS 17 TO 40



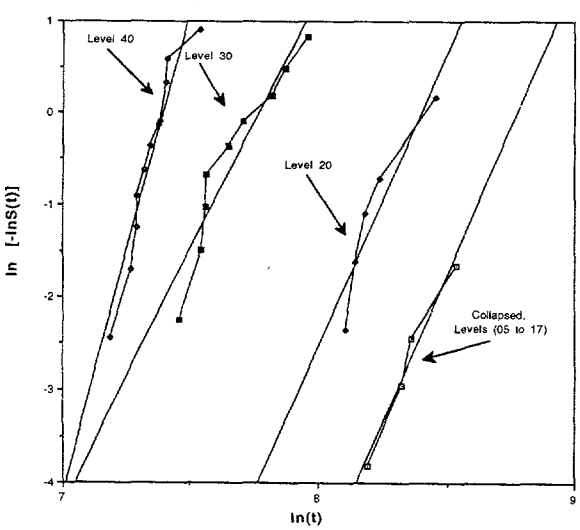
$y_{17} = -29.118 + 3.5005\ x \quad (r^2 = 0.962)$

$y_{20} = -45.034 + 5.4190\ x \quad (r^2 = 0.965)$

$y_{30} = -40.545 + 5.2342\ x \quad (r^2 = 0.928)$

$y_{40} = -77.500 + 10.477\ x \quad (r^2 = 0.913)$

FAILURE IS DEATH WITH BONE TUMOR



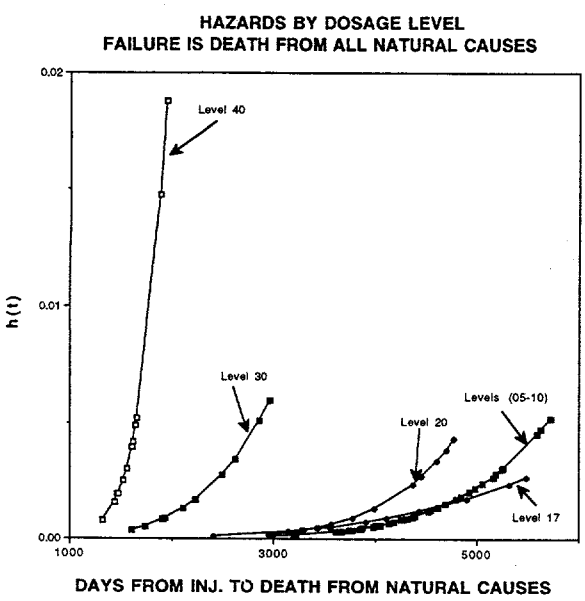
$y_{coll} = -55.878 + 6.3664\ x \quad (r^2 = 0.971)$

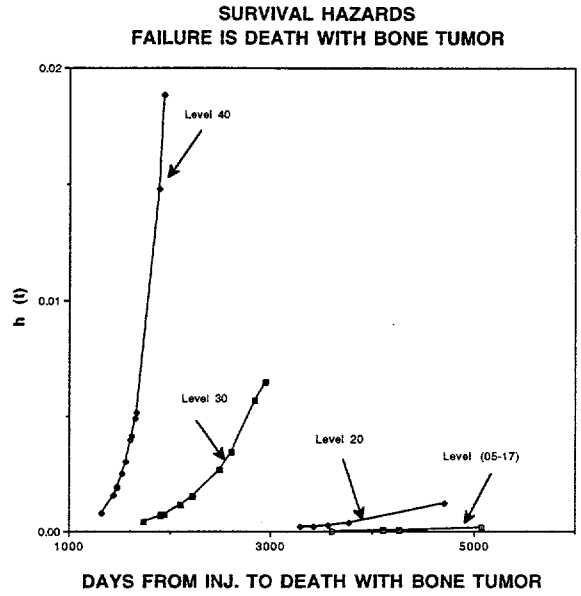
$y_{20} = -53.113 + 6.3233\ x \quad (r^2 = 0.877)$

$y_{30} = -43.224 + 5.5634\ x \quad (r^2 = 0.898)$

$y_{40} = -76.852 + 10.386\ x \quad (r^2 = 0.916)$

Fig 2





Exponential Presentation of Hazard Functions

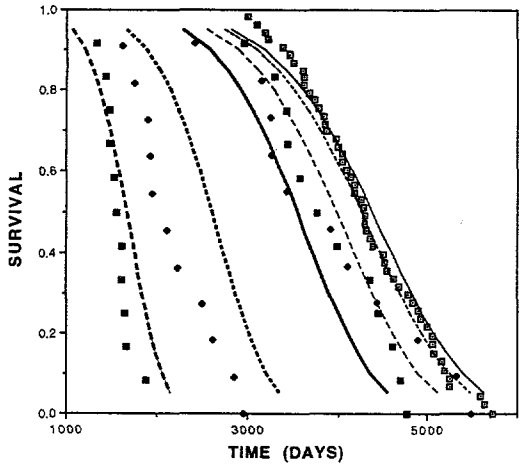
Survival Hazards

$h(t)_{contr}$	= .000001566 * exp(.0014497 * t)	r^2 = .991
$h(t)_{05-10}$	= .000001549 * exp(.0014520 * t)	r^2 = .991
$h(t)_{17}$	= .000014830 * exp(.0009672 * t)	r^2 = .984
$h(t)_{20}$	= .000001246 * exp(.0017190 * t)	r^2 = .996
$h(t)_{30}$	= .000017450 * exp(.0020088 * t)	r^2 = .993
$h(t)_{40}$	= .000001108 * exp(.0050646 * t)	r^2 = .996

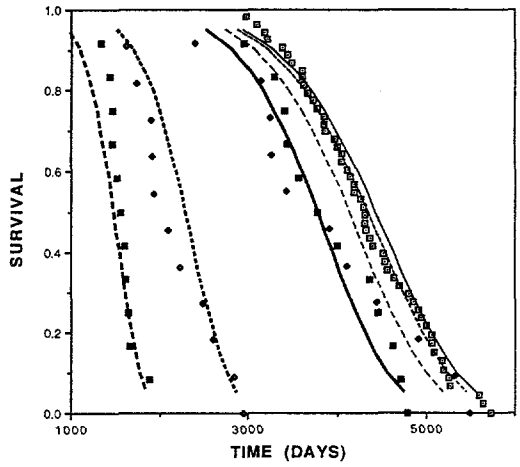
Bone Tumor Hazards

$h(t)_{05-17}$	= .000000206 * exp (.00132 * t)	r^2 = .997
$h(t)_{20}$	= .000002687 * exp (.00123 * t)	r^2 = .998
$h(t)_{30}$	= .000001705 * exp (.00220 * t)	r^2 = .996
$h(t)_{40}$	= .000001110 * exp (.00506 * t)	r^2 = .996

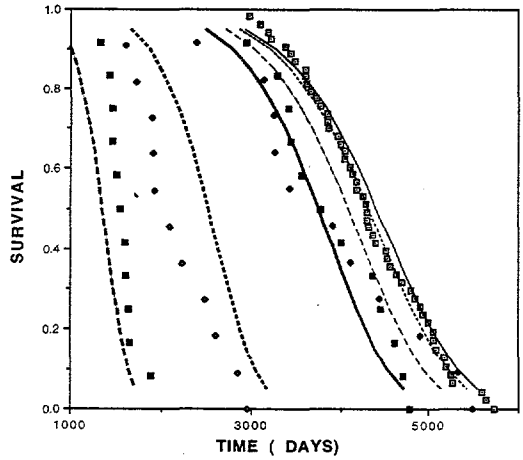
POSTINJECTION SURVIVAL WITH DSK AND DSKSQ IN MODEL



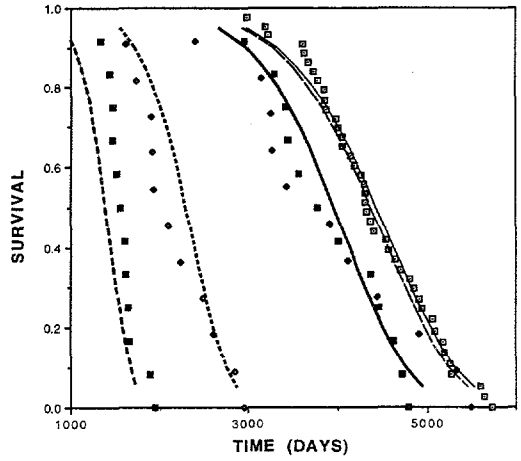
POSTINJECTION SURVIVAL WITH RATE AND RATESQ IN MODEL



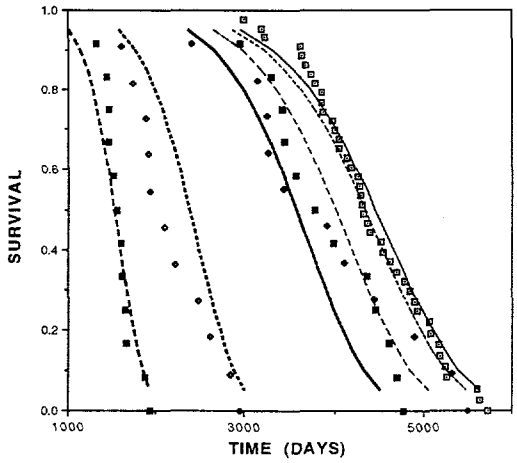
POSTINJECTION SURVIVAL WITH RATE, DSK AND DSKSQ IN MODEL



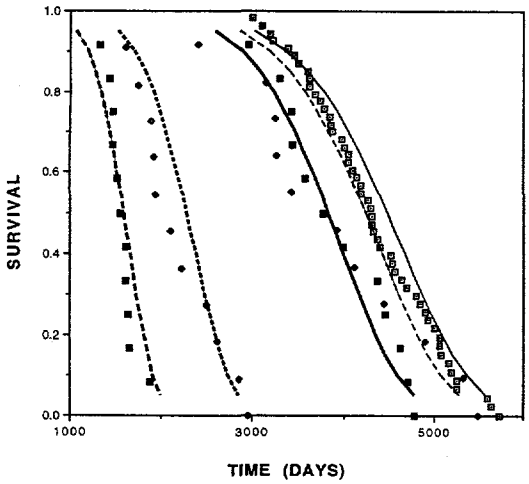
POSTINJECTION SURVIVAL WITH DSK, RATE AND RATESQ IN MODEL



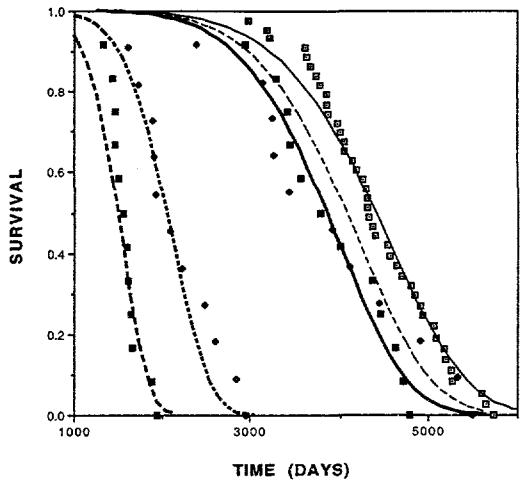
POSTINJECTION SURVIVAL WITH kBq/kg AND ITS SQUARE IN MODEL



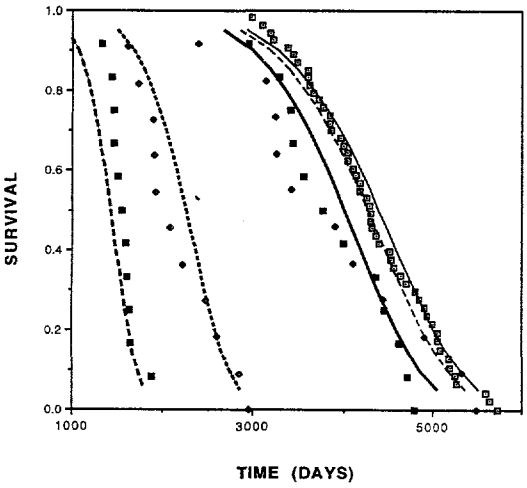
POSTINJECTION SURVIVAL WITH DSK, DSKSQ. AND GROUPS IN MODEL



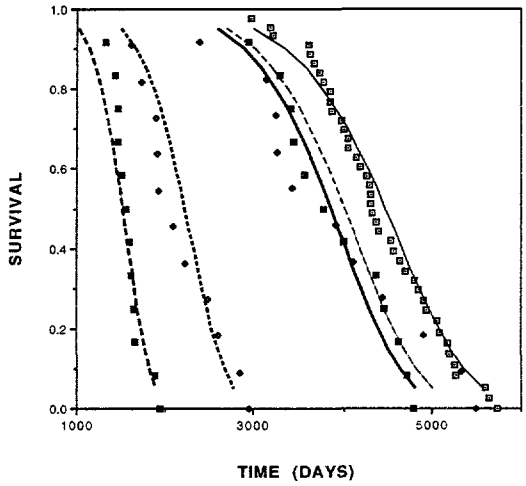
POSTINJECTION SURVIVAL WITH RATE, RATESQ. AND GROUPS IN MODEL



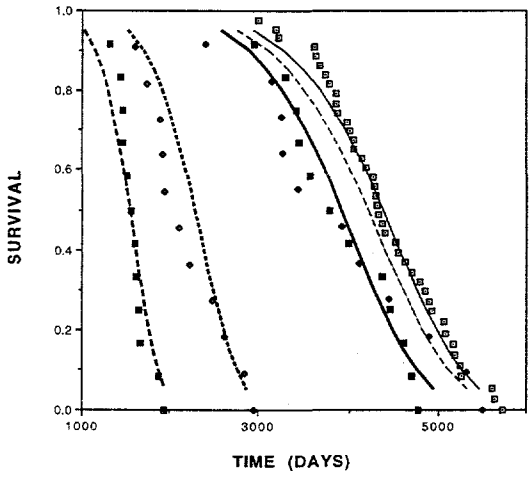
POSTINJECTION SURVIVAL WITH DSK*GROUP AND DSKSQ. IN MODEL



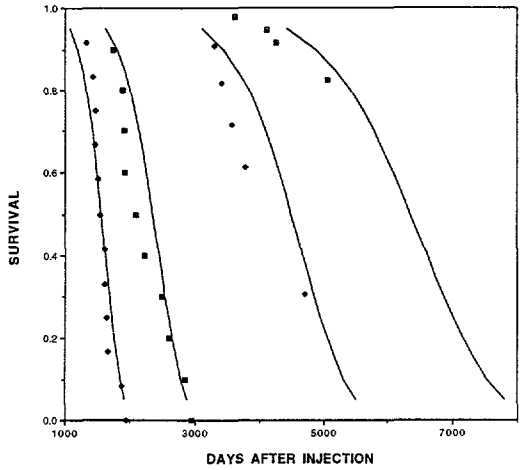
POSTINJECTION SURVIVAL WITH RATE*GROUP AND RATESQ.IN MODEL



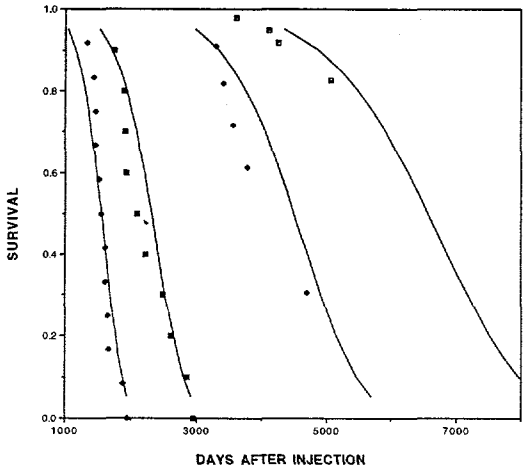
POSTINJECTION SURVIVAL WITH ONLY GROUPS IN MODEL



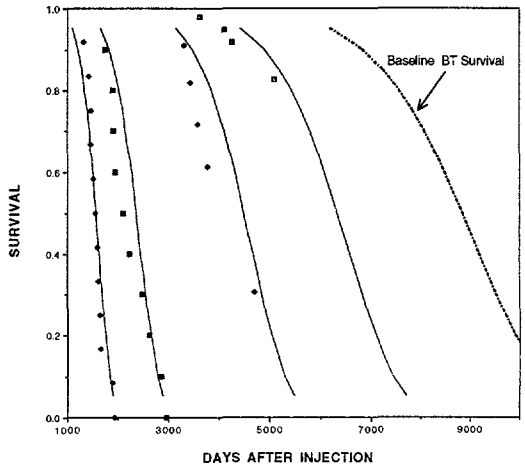
TREAT2 STAT=BT REFERENCE: RA30
LEV (LE 40 AND GE 05) IN MODEL



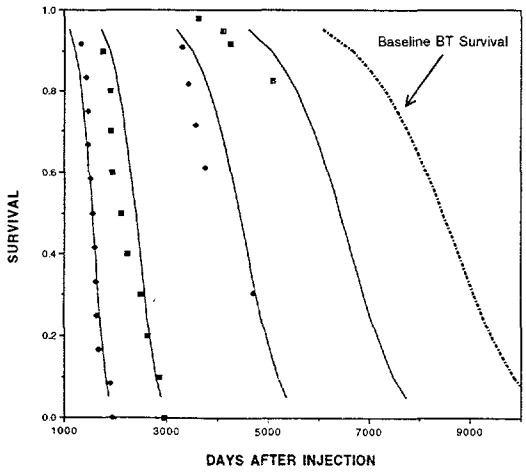
TREAT1, STAT=STAT TREAT2, STAT=BT
INDIVIDUAL LEVELS VS.CONTROL



TREAT1 AND TREAT2 (LEV LE 40)
STAT=BT



0.1 DSK, DSKSQ AND GROUPS IN MODEL TREAT1
AND TREAT2: STAT=BT



TREAT1 AND TREAT2, STAT=BT, RATE,
RATESQ AND GROUPS IN MODEL

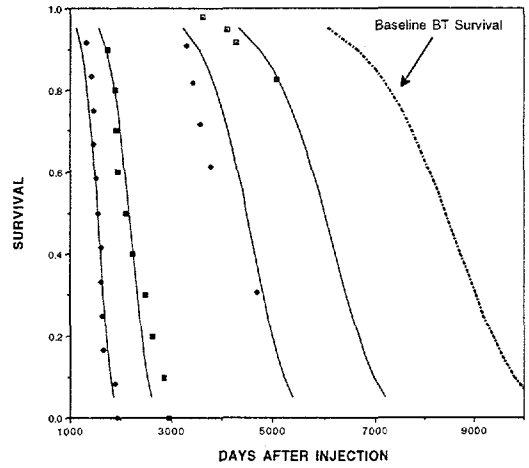


Fig 6