Dose-Response Analyses of Bone Cancers from Radium

An alternative analysis of the data reported by Raabe, Book, and Parks (*1*) leads to much greater estimates of the risk from bone cancer at low dose rates. First, a comment on their analysis is needed.

Raabe *et al.* estimate a median and standard deviation of time until death for the population of control dogs, even though fewer than 25 percent are reported to have died. If the basis for the estimates is an exact lognormal distribution of death times, the estimates are extremely sensitive to this assumption. Raabe *et al.* also assume that, for a fixed average daily dose rate $\bar{D}$, ln t (t is time to death) is normally distributed about ln $K - S \ln \bar{D}$ [K and S from Eq. 2 in (*1*)], with variance independent of $\bar{D}$. If this were true, the least-squares analysis requires that all subjects are observed until they contract bone cancer. Deaths from other causes or live withdrawals from the study would lead to biased estimates.

Raabe *et al.* find a relation between response ratio values, as measured by the estimates of K and life expectancies, L, for man ($K = 9000$, $L = 70$), beagle ($K = 2500$, $L = 15$), and mouse ($K = 850$, $L = 2$). For the three corresponding pairs, a correlation coefficient $r = .9999$ ($P < .01$) is obtained, although all six numbers were estimated independently to accuracies of no better than 5 or 10 percent. This is an inappropriate use of the correlation coefficient as a test for a linear relation. The phrase $P < .01$ (or standard errors for the slope and intercept) is also inappropriate since the three species were drawn from populations whose values of K and L do not have a bivariate normal distribution. The high correlation observed is primarily an artifact, since practically any variables relevant to the scales of man, beagle, and mouse will show up as highly correlated. For example, if the value of K for man, estimated as 9,000 by the authors, were changed to any value in the range 6,000 to 35,000, the correlation between the two variables is still .990 or greater. Thus the canine and mouse data could explain a wide range of human response data.

In reanalyzing the data, the years of exposure of each subject and the effect of competing risks on survival were taken into account. The usual epidemiological survival curve models (*2*) treat the hazard rate, or instantaneous probability (p) of death as a function of time, as the basic quantity to be estimated. If T is the time of death due to a particular risk (such as bone cancer) initiated at time $t = 0$, then, in the absence of competing risks

$$p(t < T \leq t + \Delta t | T > t) = h(t)\,(\Delta t)$$

$$p(T > t) = \exp\{-\int_0^t h(s)ds\}$$

where h is the hazard rate at time t or s. A plausible model for the hazard of carcinogenesis due to ionizing radiation (*3*) is that $h(t)$ is proportional to the cumulative dose received by time $t - a$, where a represents the latency period for development of the cancer. For a cohort exposed to a constant dose rate $\bar{D}$ (rad/day) sufficiently high so that bone cancers occurring naturally are negligible by comparison, the simplest model is

$$h(t) = b\,\bar{D}(t - a)$$

$$p(T > t) = \exp - \{\tfrac{1}{2} b\,\bar{D}(t - a)^2\}$$

where $t > a$ and a and b are constants to be estimated from the data. Maximum likelihood methods are available (*4*) to do this, but a relatively simple method can be based on the above equation. If t_m is the median time (in days) until death by bone cancer for a cohort of individuals exposed at dose rate $\bar{D}$, then

$$-\ln p(T > t_m) = \ln 2 = \tfrac{1}{2} b\,\bar{D}(t_m - a)^2$$

$$t_m = a + b'\,\bar{D}^{-1/2}$$

where $b' = (2 \ln 2/b)^{1/2}$. Figure 1 shows t_m plotted as a function of $\bar{D}^{-1/2}$ (*5*) for the three data sets analyzed in (*1*), as well as a straight line fit to each (*6*). The fitted lines lead to the following survival functions: for man, $-\ln p(T > t) = .00484\ \bar{D}(t - 13.1)^2$; for beagle, $-\ln p(T > t) = .0268\ \bar{D}(t - 1.91)^2$; and for mouse, $-\ln p(T > t) = .253\ \bar{D}(t - 0.624)^2$. Dose rate is $\bar{D}$ in rads per day, but t is measured in years. These estimates lead to practical thresholds from 20 to 40 times lower than those computed in (*1*). For example, in man, at the maximum permissible industrial bone burden of $\bar{D} = 0.0082$ rad/day, over 5 percent of those who would otherwise survive to $t = 50$ years are predicted to die of bone cancer; Raabe *et al.* predict only 1 in 400 (*7*). Their assumption of a lognormal distribution of survival times, rather than the Weibull distribution used here, leads to a very different estimate of when the first few percent of the cancers would occur, even if the same median survival times had been assumed. Unless strong evidence exists to the contrary, the usual procedure of assuming a relatively simple model for the hazard function seems advisable.

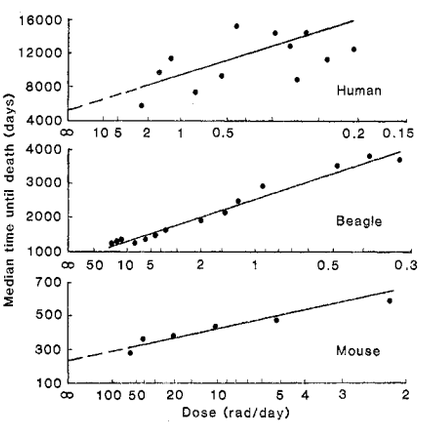

Fig. 1. Median time until death as a function of average dose rate when dose is plotted on a reciprocal square-root scale; data from Raabe *et al.* (*1*) as described in (*5*). Human and beagle data refer to deaths from bone tumors; the mouse data include deaths from all causes. The time intercepts of the fitted lines are estimates of an assumed latency period between initiation of the tumor process and time of death.

The above model is not necessarily correct. Another relatively simple model is the quadratic dose-response model, in which the hazard rate is expressed as

$$h(t) = b\,\bar{D}^2\,(t - a)^2$$

$$p(T > t) = \exp\{-b\,\bar{D}^2\,(t - a)^3/3\}$$

This model leads to a prediction of median survival time (in the absence of competing risks) of

$$t_m = a + b'\,\bar{D}^{-2/3}$$

where $b' = (3 \ln 2/b)^{1/3}$. When this relationship is fitted to the data in Fig. 1 (*8*), the estimated survival functions are $-\ln p(T > t) = .000977\ \bar{D}^2(t - 15.6)^3$ for man; $-\ln p(T > t) = .00870\ \bar{D}^2(t - 2.57)^3$ for beagle; and $-\ln p(T > t) = .0830\,\bar{D}^2\,(t - 0.704)^3$ for mouse, with the time scale shifted to years. Low dose extrapolations from this quadratic response model yield predicted effects close to those of the lognormal model of Raabe *et al.* (*1*). However, it should be noted that for all three species the latency interval estimated by the quadratic model is longer than the observed time until death from bone cancer for some individuals.

The low dose extrapolation dilemma, in which several models fit the available data tolerably well but lead to very different predictions in the low dose range, cannot be wholly resolved by statistical analyses. Even more sophisticated analyses will not change the fact that data with very few cancers in the low dose

0036-8075/81/1009-0206$01.00/0

range cannot reliably be used to predict effects in that range without more knowledge of the mechanisms of carcinogenesis.

WILLIAM H. DUMOUCHEL
Department of Mathematics, Massachusetts Institute of Technology, Cambridge 02139

References and Notes

1. O. G. Raabe, S. A. Book, N. J. Parks, *Science* **208**, 61 (1980).
2. J. D. Kalbfleisch and R. L. Prentice, *Statistical Analysis of Failure Time Data* (Wiley, New York, 1980).
3. See for example, the absolute risk model [National Research Council, "Effects on populations of exposure to low levels of ionizing radiation" (BEIR Report PB 239, Washington, D.C., 1972), p. 171] and the recent analyses [M. Ichinaru, "Multiple myeloma among atomic bomb survivors, Hiroshima and Nagasaki, 1950–76" (Technical report 9-79, Radiation Effects Research Foundation, Hiroshima, Japan, 1979)].
4. D. R. Cox, *J. R. Stat. Soc.* **B34**, 187 (1972).
5. The data for people are from figure 2 of (*1*); t_m is the median time to death for groups of three, taken in increasing order of average dose. The data for beagles are from figure 1 of (*1*), and t_m is the estimated median time to death by bone tumor of groups of approximately ten dogs, when all dogs with exposures ≥ 0.2 rad/day are taken in increasing order of dose. Within each group of dogs, t_m was estimated by the Kaplan-Meier or product-limit method to adjust for the effect of competing risks. The data for mice are from figure 2 of (*1*) for groups with doses > 2 rad/day.
6. The probability model used suggests a weighted least squares fit with weights equal to $\bar{D}$. Parameter estimates were:

Species	$a \pm$ S.E.	$b' \pm$ S.E.	R^2 (weighted)
Man	4768 ± 1732	4368 ± 1470	.469
Beagle	696 ± 46	1855 ± 105	.963
Mouse	228 ± 29	604 ± 140	.823

There seems to be a slight but systematic pattern in the deviations of the median times from the fitted line in the beagle data. For the mouse data, and to a lesser extent in the human data, the value of t_m in the highest dose group fits the straight-line model poorly. Since the mouse data relate to all causes of death, not just bone cancer, the increased mortality observed in the group receiving 60 rad/day may be due to causes for which the latent-period model is not applicable. If this point is dropped and the weighted least squares recomputed for the mouse data, the R^2 increases to .991 and $a = 286 \pm 6$, $b' = 437 \pm 24$, and $\ln p(T > t) = .484\,\bar{D}(t - 0.784)^2$. The result is an even greater effect predicted at low doses over long periods of time.
7. This calculation, which is illustrative only, is difficult because the population of those exposed was not randomly sampled, dose estimates were often made many years after the fact, more than one isotope is involved, and so forth. See R. E. Rowland, A. F. Stehney, H. F. Lucas, Jr. ["Radium related malignancies of female dial workers" (Center for Human Radiobiology, Argonne National Laboratory, Argonne, Ill., 1977)]. In fact, even a 1/400 risk by age 70 is not small by many regulatory standards.
8. A weighted least squares fit to this model, with all the points in Fig. 1 and with weights = $\bar{D}^{4/3}$, yielded:

Species	$a \pm$ S.E.	$b' \pm$ S.E.	R^2 (weighted)
Man	5705 ± 1371	3255 ± 1188	.455
Beagle	939 ± 26	1570 ± 88	.963
Mouse	257 ± 27	741 ± 237	.710

6 May 1980; revised 6 November 1980

The use of "species-dependent response ratios" by Raabe *et al.* (*1*) leads to the impression that the female CF_1 mice and Davis beagle dogs they studied were considerably more susceptible to radiogenic bone cancer than were a group of humans, primarily women. These dose ratios are based on a comparison of cumulative radiation doses absorbed at the same average dose rate to produce an equivalent biological response, death from bone cancer. Figure 2 of Raabe *et al.* (*1*) shows that an average dose rate to the skeleton of 2 rad/day, for example, which would have little or no observable effect on the life expectancy of a mouse, might kill a dog within a few years, and a young woman in about 10 to 20 years. The woman would be expected to live longer than the dog or mouse and, therefore, at time of death, to have absorbed more total radiation. The decrease in life expectancy, however, would be profoundly greater for the woman than for the other species.

I suggest that species response comparisons be based on a measure that accounts for the effect on life expectancy. One such measure can be obtained from Eq. 2 of Raabe *et al.* (*1*) by normalization of the time-death function, t, with respect to the nominal life expectancies, T, of 70, 15, and 2 years for humans, beagles, and mice

$$\Theta = \frac{t}{T} = \frac{K}{T}\,\bar{D}^{-S}$$

where $\bar{D}$ is the average dose rate to the skeleton and K and S are the parameters described in (*1*). A plot of K/T as a function of assumed body weights of 60, 10, and 0.030 kg on log-log paper shows that the dimensionless time until death, Θ, exhibits a -0.16-power dependence on body weight, B, for a fixed average dose rate to the skeleton, $\bar{D}$. The exponent obtained would be only slightly different if skeleton weight were used in place of body weight. If B is measured in kilograms, $\bar{D}$ in rad/day, and S is chosen equal to 0.29, consistent with Raabe *et al.* (*1*), the transformed equation has the form

$$\Theta = 0.67\,B^{-0.16}\bar{D}^{-0.29}$$

Then, if comparisons are made at a constant value of Θ

$$\bar{D} \sim B^{-0.55}$$

which would lead to the conclusion that man is much more sensitive to long-term exposure than are the laboratory animals. A 30-g mouse would require a dose rate 65 times as high as the dose rate to a 60-kg woman to produce the same expected fractional time to death. Since the nominal life expectancy of humans is about 35 times that of mice, the cumulative dose (rads) would only differ by a factor of about 2.

These observations are pertinent to the continuing debate on the use of laboratory data on chemical carcinogenesis to predict risk to man. Much of this debate derives from the recognition that many foreign chemicals are metabolized to more toxic forms in the body and that their ultimate effect is mediated by a complex set of pharmacokinetic factors including physiological processes, biochemical reactions, and physicochemical interactions (*2*). While both species differences and similarities (*3*) in pharmacokinetics have been stressed, pharmacokinetic properties are often measurable or predictable. Studies of tumors caused by ionizing radiation bypass any requirement for chemical activation of a carcinogen, and such tumors may display the intrinsic biological sensitivity more directly. This information could be used, then, in conjunction with pharmacokinetic studies to strengthen confidence in quantitative risk assessment.

ROBERT L. DEDRICK
National Institutes of Health, Bethesda, Maryland 20205

References

1. O. G. Raabe, S. A. Book, N. J. Parks, *Science* **208**, 61 (1980).
2. J. R. Gillette, *Clin. Toxicol.* **9**, 709 (1976); P. J. Gehring and G. E. Blau, *J. Environ. Pathol. Toxicol.* **1**, 163 (1977); R. L. Dedrick, *Environ. Health Perspect.* **28**, 311 (1979).
3. R. L. Dedrick and K. B. Bischoff, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **39**, 54 (1980).

10 June 1980; revised 10 March 1981

The Weibull function models proposed by DuMouchel are structured without reference to the data variance and fit only for median risk estimates, not for the observed distribution of bone cancer cases. For example, the distribution of cases for beagles is not properly described by

$$-\ln p(T > t) = 0.0268\,\bar{D}\,(t - 1.91)^2 \quad (1)$$

When p is .1 to .9, the function should yield a range of values that includes only about 80 percent of the cases, but in fact 99 percent (115 of 116) are within this range (Fig. 1). Of the 34 beagles with skeletal exposure dose rates between 0.04 and 0.2 rad/day (*1*), DuMouchel's model predicts that three will die of bone cancer before day 4300 for 0.04 rad/day or before day 2300 for 0.2 rad/day. No such deaths were observed, indicating that risk is overestimated. This model is rejected by a chi-square test ($P < .001$) (*2*).

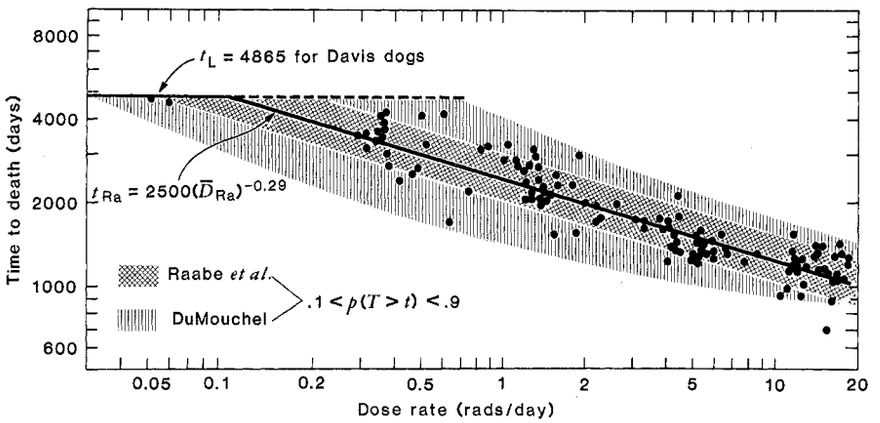

Fig. 1. Distribution of bone cancer deaths from ^{226}Ra in beagles plotted as a function of time to death and average radiation dose rate to skeleton for each dog; the predicted boundaries of 80 percent of the cases are given for the Raabe lognormal model and the Weibull function model proposed by DuMouchel.

In the Weibull function models, except DuMouchel's model for dogs (Fig. 1), the proposed fixed latency period (subtracted from t) exceeds the times of death of several individuals exposed at high dose rates. Thus, these latency periods are impossible. Further, these functions tend to narrow at high dose rates to yield small ranges of possible times to death after exposure and asymptotically approach an impossible single time for all deaths. Hence, since the DuMouchel models do not describe the actual distribution of observed cases of bone cancer deaths from skeletally deposited ^{226}Ra, they cannot be considered reliable for extrapolation to lower dose rates and risk estimation.

In contrast, the lognormal model we proposed (*1*) develops naturally from the data. The 80 percent range for this model is plotted for comparison (Fig. 1) from the relationship given by Raabe *et al.* (*3*)

$$\ln t = \ln K_m + Z \ln \sigma_g - S \ln \bar{D} \quad (2)$$

where K_m is the median value of K, the dose-response power function coefficient; $\bar{D}$ and t are the average dose rate and time combination giving a cumulative risk associated with a standardized normal deviate Z with appropriate sign, and Z is taken as $\pm$ 1.282 for the 80 percent range with $p(T > t)$ from .1 to .9. The lognormal model is a satisfactory representation of the data and is not rejected by a chi-square test at the 10 percent significance level (*2*).

The lognormal model fits the data reasonably well over all dose rates and tends to explain the relationship of the effects in people and mice (in spite of shortcomings in the data) when compared to the more precise beagle data.

The median time to death for unexposed dogs living longer than 3000 days was estimated for illustrative and extrapolation purposes. The exact value used is not crucial to the context or the dose-response functions.

Competing risks are a problem when the underlying risk distribution is estimated from the occurrence of individual cases. The methods used by Raabe *et al.* (*1*, *3*) were based on high incidences among exposed dogs and mice and on the observed concurrence of risks among exposed people. The evaluation of the risk distribution from individual cases has the desirable feature of providing direct observations of the distribution of cases.

It is not unreasonable to perform a simple linear regression on the relation of the median of K and the approximate life expectancy L (years) for the three species, since the normal law of errors is approximated for lognormal errors that have small geometric standard deviations. The resultant excellent fit is surprising and fortuitous

$$K_m = (655 \pm 57) + (119 \pm 1)\, L \quad (3)$$

An F test of variance shows that the value of K_m observed to be 9,000 for man has to be between 8,850 and 10,250 for acceptance at the 1 percent significance level, and the correlation coefficient is larger than .99 even at the 5 percent significance level.

The suggestion by Dedrick that people are more sensitive or more susceptible to bone cancer from skeletal irradiation by ^{226}Ra represents a viewpoint different from that of Raabe *et al.* (*1*, *3*). The computation by Dedrick involving body mass is not needed, since this issue can be addressed through Eq. 3 by dividing by the life expectancy and substituting the power function dose-response relationship (*1*) to yield

$$\frac{t_m}{L} = \left(\frac{655}{L} + 119\right) \bar{D}^{-S} \quad (4)$$

where S is the observed logarithmic slope, assumed to be 0.29 for all three species, and t_m is the median time (days) to death from bone cancer. Clearly, small values of this ratio t_m/L, representing life-shortening, occur at any given dose rate for species with long natural life expectancies. However, it is important to note that this is the case only if the exposure begins at birth or occurs for the same fraction of life span (and if the same dose-response relationships hold for other exposure times). In fact, the life expectancy used in Eq. 3 (*3*) is probably a surrogate for a more appropriate underlying cellular metabolic rate that differs for the bone cells of the three species and is about proportional to observed life expectancy. Life expectancy itself is not fixed. It seems more meaningful to describe interspecies relative biological sensitivity as the ratio of cumulative doses in different species that yield the same risk, assuming no maximum life span (*3*). Then it is seen that it takes about ten times longer and ten times more total absorbed radiation in a human skeleton than in a mouse skeleton to yield the same risk level in both species, if they both have the same average concentration of radium in their bones.

OTTO G. RAABE
Laboratory for Energy-Related Health Research, University of California, Davis 95616

References and Notes

1. O. G. Raabe, S. A. Book, N. J. Parks, *Science* **208**, 61 (1980).
2. Chi-square test of the distribution of beagle bone tumor deaths from ^{226}Ra in the skeleton for the lognormal model of Raabe *et al.* (*1*, *3*) and the model of DuMouchel. At the 10 percent significance level with one degree of freedom, the chi-square should be less than 2.7.

$p(T > t)$	Expected	Raabe model	DuMouchel Model
< .1	11.6	11 (0.03)*	0 (11.6)
.1 to .5	46.4	40 (0.88)	49 (0.15)
.5 to .9	46.4	53 (0.94)	66 (8.28)
> .9	11.6	12 (0.01)	1 (9.69)
Total	116	116 (1.9)	116 (29.7†)

*Numbers in parentheses are the chi-square values. †$P < .001$.

3. O. G. Raabe, S. A. Book, N. J. Parks, *Health Phys.* **40**, 863 (1981).

13 July 1981