CONF-8705116--2

CONF-8705116--2

DE87 009680

Prediction of the Mortality Dose-Response Relationship in Man[1]

M. D. Morris and T. D. Jones
Engineering Physics and Mathematics, and Health and Safety Research Divisions
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

Abstract

Based upon an extensive data base including 100 separate animal studies, an estimate of the mortality dose-response relationship due to continuous photon radiation is predicted for 70 kg man. The model used in this prediction exercise includes fixed terms accounting for effects of body weight and dose rate, and random terms accounting for inter- and intra-species variation and experimental error. Point predictions and 95% prediction intervals are given for the LD_{05}, LD_{10}, LD_{25}, LD_{50}, LD_{75}, LD_{90}, and LD_{95}, for dose rates ranging from 1 to 50 R/min.

1. This work sponsored by the Defense Nuclear Agency under Task Code U99QMXMH and Work Unit Code 00018 of IACRO DNA 85-903 with the U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

EHB

Prediction of the Mortality Dose-Response Relationship in Man

The data used in this exercise were taken from various animal experiments which were carried out to examine the effects of continuous or nearly continuous exposures to photon radiation. An extensive summary of 211 such experiments was reported in Jones, et al. (1986), which served as our initial data source. Of the studies included in that summary, 104 were published in detailed enough form to permit estimation of the mortality dose-response curve. Of these, three were not used due to the apparent presence of excess background mortality. Also, one other study, Cronkite, et al. (1955), was not included because the dose rate used in that experiment (approximately 10^5 R/min.) was more than 100 times greater than that in any other available experiment. The remaining 100 experiments span 13 species and dose rates of from .22 R/min. to 800 R/min.; a tabulation of experiments by species and dose rate is given in Table 1.

For each of the 100 experiments, the mortality dose-response function was estimated using an assumed probit model, i.e.

$$r = \Phi\left[\gamma(d - LD_{50})\right],$$

where d is the dose in cGy to bone marrow, Φ is the cumulative standard normal distribution function, and r is the resulting proportion of mortality. γ and LD_{50} are unknown parameters which uniquely specify the dose-response function; we estimate these from the data for each experiment. The rationale for use of the probit model is given in detail in Morris and Jones (1986). In that work, seven two-parameter models used in quantal dose-response analysis were compared for goodness of fit, using essentially the same data set as in the present work. The probit model in untransformed dose was shown to be one of the more accurate functional forms, especially in the tail regions of relatively high and low mortality.

For each experiment, maximum likelihood estimates of LD_{50} and γ (i.e., slope) were computed, along with their asymptotic standard errors and correlation. In the following, we will describe a statistical procedure based on these LD_{50} estimates to predict LD_{50} values for man. Since the probit curve is completely specified by the parameter values of γ and LD_{50}, any other dose corresponding to a specified level of mortality is a simple function of these two parameters. In

fact:

$$LD_x = LD_{50} + Z_x / \gamma,$$

where x is any value greater than 0 and less than 100, and Z_x is the x-th percentile of the standard normal distribution. By substituting the maximum likelihood estimates of γ and LD_{50} in the right side of the above equation, the maximum likelihood estimate of the desired dose can be calculated, and standard errors of these can also be easily obtained. Besides the LD_{50}, we have also modeled values of the LD_{05}, LD_{10}, LD_{25}, LD_{75}, LD_{90}, and LD_{95}, and calculated prediction intervals for each of these in man.

Modeling Lethal Dose Levels

In the following, we will describe our modeling and prediction procedure for the LD_{50}. The same procedure was followed for the other 6 levels of mortality mentioned above.

In Table 2 we list, by dose rate and species, average values of the LD_{50} estimates from the 100 experiments. Two well known patterns are easily seen in the data. First, within each species, higher dose rates are generally associated with lower values of LD_{50}. The exceptions to this pattern in the table can quite easily be explained by small sample sizes and random noise. Second, species of larger body weight tend to have lower values of LD_{50} at any dose rate. We have found that, in this data set, the logarithms of body weight, dose rate, and LD_{50} are empirically well related through a linear functional form, i.e.

$$\ln(LD_{50}) \approx \alpha + \beta_w \ln(\text{body weight}) + \beta_r \ln(\text{dose rate}).$$

If the above equation is fitted to the data by ordinary least-squares, estimates of the three coefficients are $\hat{\alpha}$=6.317, $\hat{\beta}_w$ =−.165, and $\hat{\beta}_r$ =−.091. (Throughout this discussion, we distinguish between an unknown constant quantity and its estimate by placing a caret (ˆ) above the estimate.)

However, linear regression analysis in this form is not an appropriate approach for modeling LD_{50}'s across species and dose rates for at least two demonstrable reasons. First, while a single equation of the above form passes through the collected data fairly well (R^2 is .74), the fitted

curve tends to over- or under-estimate LD_{50}'s for individual species. For example, of the 11 experiments using dogs as experimental units, the model fitted by ordinary least-squares overestimates 10 of the LD_{50}'s. Hence, while body weight is a useful surrogate variable for species, it is clear that some of the intra-species variation cannot be explained by this variable.

A second difficulty is related to inter-species variation. Ordinary regression analysis is based on an assumption that all values of the observed variable (natural log of LD_{50}) are measured with equal precision. The standard errors which can be computed for each experiment are clear evidence that this is not the case: for example, experiments employing larger numbers of animals typically have relatively smaller standard errors of estimation. Also, while the standard errors associated with each $\ln(LD_{50})$ represent the variation in estimation that would be expected if *that* experiment were repeated, this does not represent total intra-species variation. For example, the average standard error of $\ln(LD_{50})$ observed over the 48 mouse studies in this data base is less than one-tenth the standard deviation of the 48 $\ln(LD_{50})$ estimates calculated.

Hence, an appropriate model for statistical analysis of these data should, in addition to including the terms in the above equation, take into account (1.) inter-species variation not explained by body weight, (2.) the varying degrees of experimental precision for differing experimental protocols, and (3.) the intra-species variation not included in experimental variation (e.g. due to strain, specific exposure conditions, measurement techniques unique to an investigator or laboratory, et cetera.). The model we have adopted to account for all of these items is a mixed linear model (see, for example, Searle, 1971) including fixed and random terms as follows:

$$\ln(\text{estimated } LD_{50}) = \alpha + \beta_w \ln(\text{body weight}) + \beta_r \ln(\text{dose rate}) + \xi_{\text{inter}} + \xi_{\text{intra}} + \epsilon,$$

where ξ_{inter} is a random variable representing inter-species variation not explained by body weight, ξ_{intra} is a random variable representing intra-species variation, and ϵ is the random imprecision, such as measurement error, which would be observed in repeated executions of the same experiment on the same strain of animal by the same investigator, et cetera.

In the mixed linear model above, α, β_w, and β_r can be thought of exactly as in the case of ordinary multiple linear regression. That is, they are fixed, unknown constants, which are presumed

to be valid across all species and experimental conditions studied. The term representing inter-species variation, ξ_{inter}, is a random quantity which varies from species to species, but is constant across the studies of a single species. Hence, it is intended to represent the deviation of an entire species from the fitted model, as with the dog experiments mentioned above. In our analysis, ξ_{inter} is assumed to be a normal random variable with mean of zero and standard deviation of δ_{inter}. This source of variation plays an important role in quantifying the uncertainty of a predicted LD_{50} in man, since it is a measure of inter-species variation after "adjustment" for body weight.

The final term in the above model, ϵ, is the random term included in ordinary linear regression models. It represents what may be called "measurement error" specific to each experiment (although in fact more than true measurement error is often represented by this term). In this case, the variability of ϵ for each experiment is different, depending upon the dose rates used, number of animals in each group, and other factors. So, we assume that ϵ is normally distributed with mean zero and standard deviation σ_{study}, which is different for each study. Fortunately, we have an "external" estimate of σ_{study} for each experiment, namely the computed standard error of each $\ln(LD_{50})$.

The intra-species variation not accounted for by ϵ is represented by the final random variable, ξ_{intra}. In the following we shall assume that each experiment has its own value of ξ_{intra}, and that these are normally distributed with mean zero and standard deviation δ_{intra}.

We have written a FORTRAN program to calculate maximum likelihood estimates of the fundamental parameters of the above model, namely α, β_w, β_r, δ_{inter}, and δ_{intra}, under the assumption that the individual values of σ_{study} can be adequately approximated by the standard error of $\ln(LD_{50})$ calculated for each experiment. Body weights used are "generic" body weights for each species, listed in Table 3. Generic body weights may be more consistent with inter-species modeling than individual body weights; e.g. Vriesendorp and vanBekkum (1984) have postulated that species body weight is well correlated with the number of hematopoietic stem cells. The same model and estimation procedure was also used to estimate the five parameters for modeling each of LD_{05}, LD_{10}, LD_{25}, LD_{75}, LD_{90}, and LD_{95}. Parameter estimates based on the 100 studies in

our data set, for each of the 7 levels of mortality, are given in Table 4.

Prediction for an Unobserved Species

Based upon the model estimates discussed above, a *prediction interval* can be established for a specified level of mortality, given a dose rate and body weight of an unobserved species. We now briefly discuss what this interval represents, and the assumptions on which it rests.

Prediction intervals and confidence intervals are similar statistical procedures for estimating, with controlled uncertainty, unknown quantities. However, they are used in different settings, depending upon the nature of the quantity being estimated. A confidence interval is an interval estimate of a single, fixed quantity (generally called a "parameter" in statistical terminology) such as β_w in our model of LD_{50}. Confidence intervals can also be placed on combinations of fixed quantities such as $\alpha + \beta_w \ln(\text{body weight}) + \beta_r \ln(\text{dose rate})$, where a body weight and dose rate have been specified; this is how the widely-used confidence bands for regression models are generated. In our case, such an interval would be an interval estimate of the log lethal dose for a specified body weight and dose rate, averaged over all potential species and subspecies of that body weight.

A prediction interval, on the other hand, is an interval estimate of a quantity which will, itself, contain a random component. This is more appropriate for our interests, since our aim is to construct estimates of doses for a particular, unobserved species of body weight 70 kg (e.g. man). Since our model includes random (unexplained) variation due to species, an interval prediction of man's LD_{50} must make allowance for the random component in the LD_{50} of man, i.e. that not explainable by body weight. For a more in-depth description of the comparison between confidence and prediction intervals in ordinary multiple linear regression, see, for example, Neter and Wasserman (1974).

For our purposes, a point prediction of the $\ln(LD_{50})$ in man is

$$\text{prediction} = \hat{\alpha} + \hat{\beta}_w \ln(70) + \hat{\beta}_r \ln(\text{dose rate}),$$

that is, the same as the estimate of $\ln(LD_{50})$ averaged over all species of that body weight. The difference between a confidence interval for the latter quantity and the prediction interval for a

single species is in the uncertainty term which is added and subtracted from this prediction. In this case, a 95% prediction interval for man's $\ln(LD_{50})$ is of form

$$\text{prediction} \pm 1.96\sqrt{\text{se}^2(\text{prediction}) + \hat{\delta}_{\text{inter}}^2}$$

where se(prediction) is the standard error of the prediction, which is in turn a function of $\hat{\delta}_{\text{inter}}$ and $\hat{\delta}_{\text{intra}}$. The prediction interval differs from the corresponding confidence interval in the appearance of $\hat{\delta}_{\text{inter}}$ under the radical sign; this effectively widens the interval to account for the unobservable species-specific deviation for man which cannot be explained by body weight. Finally, recall that this is actually a prediction interval for the log of the dose which results in 50% mortality; the prediction interval for the dose itself is found by simply taking the antilog of these interval endpoints.

The interpretation for a rate-specific LD_{50} prediction interval obtained as above is as follows. Assuming that our basic model of 3 fixed and 3 random effects is adequate, that the 13 species thus far collected are associated with 13 independent values of ξ_{inter}, and that man would represent another similar "random draw" from this collection of species, a prediction interval of the type described here would contain the true LD_{50} for man with probability .95.

Table 5 contains point predictions and 95% prediction intervals for doses corresponding to seven levels of mortality, at varying dose rates for a 70 kg man. At first glance, these intervals may appear to be surprisingly wide. This is due to the appearance of the $\hat{\delta}_{\text{inter}}$ term in the prediction interval formula. As sample sizes increase, the terms which constitute se(prediction) become small, approaching zero in the limit. Thus, for confidence intervals, the width of the interval can be reduced without bound by increasing sample sizes. This is not true for prediction intervals, where uncertainty due to the random component of the predicted quantity must continue to be considered, and is not reduced by increasing the amount of available data. Of the species represented in our data set, goats, sheep, and swine have body weights closest to that of man (each is 60 kg). As shown in Table 1, none of these species appeared in experiments with dose rates of over 50 R/min. Therefore, we suggest that our model, based upon the present data, not be used to predict doses for man outside of the range of dose rates from one to fifty R/min.

References

Cronkite, E.P., V.P. Bond, R.H. Lee, and W.H. Chapmen. 1955. The Relative Biological Effectiveness of Atomic Bomb Gamma Radiation in Mice. Research Rep. Project NM006012.04.86, vol. 13, pp. 89-112, Naval Medical Research Institute, Naval Medical Center, Bethesda, Maryland.

Jones, T.D., M.D. Morris, S.M. Wells, and R.W. Young. 1986. Animal Mortality Resulting from Uniform Exposures to Photon Radiations: Calculated LD_{50}'s and a Compilation of Experimental Data. Technical Report ORNL-6338, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Morris, M.D., and T.D. Jones. 1986. Human Response to Nuclear Radiation Environments. Progress Report on IACRO DNA 85-903.

Neter, J. and W. Wasserman. 1974. Applied Linear Statistical Models. Richard D. Irwin, Inc., Homewood, Illinois.

Searle, S.R. 1971. Linear Models. John Wiley and Sons, New York.

Vriesendorp, H.M. and D.W. van Bekkum. 1984. "Susceptibility to Total Body Irradiation". In: Response of Different Species to Total Body Irradiation, ed. J.J. Broersa and T.J. McVittie. Martinus Nijhoff, Boston.

Table 1: Individual Studies by Species and Dose Rate.

Species	Dose Rate (R/min.)					
	<1	$\geqslant 1$ and <5	$\geqslant 5$ and <10	$\geqslant 10$ and <50	$\geqslant 50$ and <100	$\geqslant 100$
Burro	3	0	1	0	0	0
Cattle	1	0	0	0	0	0
Chinchilla	0	0	0	1	0	0
Dog	0	0	5	5	1	0
G. Pig	0	1	0	2	0	0
Goat	0	0	1	1	0	0
Hamster	0	0	0	1	0	0
Mouse	2	16	2	13	13	2
Primate	0	2	0	5	0	1
Rabbit	1	0	0	0	0	1
Rat	0	1	0	11	0	0
Sheep	0	0	2	1	0	0
Swine	1	0	1	2	0	0

Table 2: Average LD_{50} (cGy to marrow) Estimates by Species and Dose Rate.

Species	Dose Rate (R/min.)					
	<1	≥ 1 and <5	≥ 5 and <10	≥ 10 and <50	≥ 50 and <100	≥ 100
Burro	295	-	180	-	-	-
Cattle	159	-	-	-	-	-
Chinchilla	-	-	-	494	-	-
Dog	-	-	287	244	230	-
G. Pig	-	251	-	296	-	-
Goat	-	-	215	232	-	-
Hamster	-	-	-	556	-	-
Mouse	1288	981	917	722	647	708
Primate	-	342	-	528	-	366
Rabbit	907	-	-	-	-	838
Rat	-	550	-	590	-	-
Sheep	-	-	180	177	-	-
Swine	379	-	277	186	-	-

Table 3: Body Weights used in Modeling.

Species	Body Weight (kg)
Mouse	0.025
Hamster	0.125
Rat	0.225
Chinchilla	0.430
G. Pig	0.500
Rabbit	3.0
Primate	5.0
Dog	10.0
Goat	60.0
Sheep	60.0
Swine	60.0
Burro	155.0
Cattle	375.0

Table 4: Parameter Estimates for Lethal Dose Models.

Lethal Dose	Parameter Estimates				
	$\hat{\alpha}$	$\hat{\beta}_w$	$\hat{\beta}_r$	$\hat{\delta}_{inter}$	$\hat{\delta}_{intra}$
LD_{05}	6.052	-.185	-.134	.368	.280
LD_{10}	6.090	-.175	-.126	.358	.264
LD_{25}	6.218	-.173	-.114	.306	.244
LD_{50}	6.352	-.173	-.100	.282	.224
LD_{75}	6.470	-.172	-.091	.284	.210
LD_{90}	6.567	-.173	-.087	.294	.200
LD_{95}	6.621	-.173	-.086	.302	.194

Table 5: Predictions of Lethal Doses (cGy to marrow) for 70 kg Man *.

Lethal Dose	Dose Rate (R/min.)					
	1	2	5	10	20	50
LD_{05}	88	80	71	65	59	53
	194	177	156	143	130	115
	427	388	343	312	284	251
LD_{10}	98	89	80	73	67	60
	210	192	171	157	144	128
	451	413	367	336	308	274
LD_{25}	125	115	104	96	89	80
	240	222	200	185	171	154
	463	427	384	355	328	295
LD_{50}	151	141	128	120	112	102
	275	257	234	218	204	186
	503	469	427	398	371	338
LD_{75}	169	159	146	137	129	119
	310	291	268	251	236	217
	569	534	490	460	431	396
LD_{90}	183	172	159	150	141	130
	341	321	297	279	263	243
	639	601	554	521	490	452
LD_{95}	189	178	165	156	147	136
	360	339	313	295	278	257
	684	644	595	560	527	487

*Note: Entries are (1.) Lower 95% prediction limit, (2.) Point prediction, and (3.) Upper 95% prediction limit.