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Dose-Response Model Selection for Animal Studies and Prediction of Human Response Levels *

Summary of Conclusions for Consensus Paper, NATO RSG V Meeting

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Abstract

Our recent work in the comparison of parametric models for use in animal radiation mortality studies is reviewed, along with predictions of lethal doses for man based on these models.

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DISCLAIMER

Dose-Response Model Selection for Animal Studies

Early investigations aimed at characterizing the mortality effects of radiation on animals primarily emphasized estimation of the LD_{50} or "mid-lethal" dose. This was natural, since the dose-response relationship is rather steep for this exposure, compared to many other biological insults, and the LD_{50} is a convenient measure of central tendency which is easily understood, and relatively insensitive to methods of estimation, including model selection. However, present interests have been widened to include modeling and predicting the entire range of mortality response; hence model selection has become a much more important issue.

We have conducted a comparison of seven commonly used two-parameter dose-response models, using the accumulated data base of animal studies reported in Jones, et al, 1986. The point of this work was not to estimate response levels themselves, but to assess the ability of each model to fit the data accurately. The models considered include: (1.) the right-skewed extreme-value model, (2.) the left-skewed extreme-value model, (3.) the log-logistic model, (4.) the log-probit model, (5.) the logistic model, (6.) the probit model, and (7.) the Weibull model. All seven functional forms were used to individually model the data from 105 separate experiments, covering 13 species of animals. The models were fit to the data by the method of maximum likelihood, and goodness of fit for each model was assessed using likelihood-based statistics and patterns of fitted residuals. The primary conclusions from this analysis are summarized below.

(1.) Each of the seven models displayed statistically significant lack of fit for the rodent studies. This is not particularly surprising, given the relatively large number of experiments on mice and rats in the data base, and the fact that these are typically larger studies (larger numbers of animals) than those which use other species. Even though 2-parameter models display statistically significant lack-of-fit when enough data are present, we believe that at least some of them may be accurate enough for biologically motivated purposes.

(2.) Based upon summary chi-square goodness of fit statistics for mouse experiments and other species pooled, the models which display the best degree of fit to the data are logistic, probit, and Weibull models, while the two extreme-value models are relatively worse in fit than the others.

(3.) For each experiment and fitted model, the number of positive and negative residuals (occurrences of observed data above and below the fitted curve) were calculated in each of 3 dose "zones" — LD_0 to LD_{25}, LD_{25} to LD_{75}, and LD_{75} to LD_{100}. The logistic and probit models displayed the best pattern of residuals in each zone, i.e. closest to a 50/50 split. The two extreme-value models, log-probit model, and Weibull model each displayed an unbalanced split of at least 60/40 in at least one zone each.

(4.) For each individual experiment, models were ranked from 1 to 7 based on the goodness of fit chi-square statistic for that experiment. The extreme-value models were most often either worst (rank 7) or best (rank 1), while the Weibull model was most often either next to worst (rank 6) or next to best (rank 2). The probit model displays the best average rank, and the probit and logit models are the only two models which are never ranked worst for any study.

Overall, we feel that the logistic and probit models do the best job of accurately modeling the variety of data included in our data base. The Weibull model would probably be our third choice, and might be preferred by some investigators for theoretical reasons.

Prediction of Human Response Levels

Based on 100 studies from the data base of animal experiments tabulated by Jones, et al. 1986, we have constructed an empirical mathematical model for predicting doses of specified lethality in man. For modeling LD_{50}'s, the model is a mixed (random and fixed effects) linear model of form:

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

where LD_{50} is expressed in cGy to bone marrow, body weight in kg, and dose rate in R/min. In this model, α, β_w, and β_r are fixed constants which have the same interpretation as the coefficients in an ordinary regression model. ξ_{inter} is a random variable, different for each species, which represents the effect of species variation which cannot be explained by body weight. ξ_{intra} is another random term, which represents variation among experiments within the same species, due to such sources as strain of animal, differing investigators and laboratory procedures, and so forth. ϵ is pure statistical or "chance" error, reflecting the variation in estimated quantities one would see if the same experiment were run repeatedly on the same strain of animal, by the same investigator, and so forth.

We have estimated the three fixed terms in the model (α, β_w, and β_r) and standard deviations of the random terms by the method of maximum likelihood. Using these estimates, we have calculated point and interval predictions of the LD_{05}, LD_{10}, LD_{25}, LD_{50}, LD_{75}, LD_{90}, and LD_{95} for a new (unobserved) species of body weight 70 kg, i.e. man. Point predictions and 95% prediction intervals for these quantities are displayed in the attached Table 1.

Reference

T.D. Jones, 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*, ORNL-6338, December, 1986.

Table 1: 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.