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STATISTICAL INFERENCE FOR THE PARAMETERS OF A TWO-STAGE DOSE-RESPONSE MODEL USING THE MINIMUM SUM OF ABSOLUTE ERRORS ESTIMATORS

by

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Palavras-Chave: Linear dose-response model, linear-quadratic dose-response model, minimum sum of absolute errors regression, Monte Carlo, multi-stage model, nonlinear model, single-stage model.

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STATISTICAL INFERENCE FOR THE PARAMETERS OF A TWO-STAGE DOSE-RESPONSE MODEL USING THE MINIMUM SUM OF ABSOLUTE ERRORS ESTIMATORS

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Abstract

In this paper, our objective is to investigate the asymptotic properties and distributions of the minimum sum of absolute MSAE estimators of the two-stage (linear-quadratic) dose response model. If the asymptotic distribution of the estimator is normal, then we determine the minimum value of N, the number of experimental units at each dose, at which we may use the normal distribution to draw statistical inferences, such as construct confidence intervals and test hypotheses, about the parameters of the model. However, if the asymptotic distribution is not normal, then we investigate whether the tails of the asymptotic and normal distribution behave alike.

Keywords : linear dose-response model, linear-quadratic dose-response model, minimum sum of absolute errors regression, Monte Carlo, multi-stage model, nonlinear model, single-stage model.

1. INTRODUCTION

The multi-stage dose-response model proposed by Armitage and Doll (1954) is:

$$P(d) = 1 - \exp(-\sum_{j=0}^{k} \alpha_j d^j), \tag{1}$$

where $P(d)$ is the probability that a cell becomes malignant at dose d of a carcinogenic, k is the number of stages and $\alpha_j \geq 0$ are the parameters, $j = 0, 1, \ldots, k$, of the model. Let y_i, $0 \leq y_i \leq 1$, denote the value of the response variable corresponding to dose d_i, $i = 1, 2, \ldots, n$, in a bioassay with N experimental units at each of the n doses. Then, the model may be written as:

$$y_i = 1 - \exp(-\sum_{j=0}^{k} \alpha_j d_i^j) + e_i, \tag{2}$$

where e_i is the unobservable random error for the i^{th} observation. To estimate the parameters of the model, the maximum likelihood and the least squares methods are often used; however, these methods are very sensitive to outliers, André, Peres, and Narula (1991). To overcome this difficulty, they proposed the minimum sum of absolute errors MSAE criterion to estimate the parameters of (2) because it is more resistant to outliers than the popular methods. Although the MSAE estimators are not robust to outliers in the factor space (leverage point), this does not cause any problems in the dose-response model because the doses are controlled.

The MSAE estimators of the parameters are obtained by minimizing

$$\sum_{i=1}^{n}|e_i| = \sum_{i=1}^{n}|y_i - 1 + \exp(-\sum_{j=0}^{k}\alpha_j d_i^j)|. \qquad (3)$$

This intrinsically nonlinear function may be solved by using any algorithm for computing the MSAE estimates of a nonlinear model, Gonin and Money (1987). To compute the estimates, André, Peres and Narula (1991,1992) proposed two algorithms which exploit the special structure of the model.

Guess, Crump and Peto (1977) and Land (1980) reported that in practical applications to chemical carcinogens and risk analyses for ionizing radiation, the multistage models have at most two stages. Recently, using Monte Carlo study, André, Narula, Peres, and Ventura (1997) have shown that the MSAE estimators of the parameters in the one-stage (k = 1) model are: asymptotically unbiased; the MSAE estimator $\hat{\alpha}_1$ is asymptotically normally distributed; and the distribution of $\hat{\alpha}_0$ approaches the normal distribution whenever α_0 is not very close to the boundary ($\alpha_0 > 0.03$) for all values of α_1 whereas for small values of α_0 ($\alpha_0 < 0.02$), the distribution of $\hat{\alpha}_0$ approaches the normal distribution only when P(1), the response at dose d = 1 = the maximum tolerated dose, is high. For more details, the interested reader may refer to André, Narula, Peres, and Ventura (1997). Based on these results, André and Narula (1997) give sample sizes for which normal distribution may be used to draw inferences about the parameter. However, the statistical properties of the MSAE estimators for the two-stage dose-response model have not been investigated yet.

In the multi-stage model (2), when k = 2, we get the two-stage (linear-quadratic) dose-response model:

$$y_i = 1 - \exp(-\alpha_0 - \alpha_1 d_i - \alpha_2 d_i^2) + e_i. \qquad (4)$$

The parameter α_0 is approximately equal to P(0); and when we set the maximum tolerated dose equal to one, $\alpha_1 + \alpha_2$ is proportional to P(1), in fact,

$$\alpha_0 \cong P(0) = 1 - \exp(-\alpha_0), \qquad (5a)$$

and

$$\alpha_1 + \alpha_2 = -\alpha_0 - \ln(1 - P(1)). \qquad (5b)$$

In this paper, our objective is to investigate the asymptotic properties and the distribution of the MSAE estimators of the two-stage dose-response model. Over the region where the estimators follow asymptotically normal distribution, we would like to determine the smallest sample size for which we may use the normal distribution to draw inference about the parameters. However, over the region where the asymptotic distribution of the MSAE estimators is not normal, we would like to investigate if the tails of the asymptotic and the normal distributions behave alike and to know the sample sizes at which normal distribution may be used to draw inference about the parameters. The rest of the paper is organized as follows: In Section 2, we describe the Monte Carlo study to determine the asymptotic properties and distribution of the MSAE estimators of the parameters of the model and the smallest sample size at which normal distribution may be used to draw inferences about the parameters. In Section 3, we present and discuss the results of the Monte Carlo study. We give an expression for the variance-covariance of the MSAE estimators in Section 4 and conclude the paper with a few remarks in Section 5.

2. THE MONTE CARLO STUDY

We set the maximum tolerated dose equal to one and fixed the number of doses n equal to five at the following values: $d_1 = 0.00$, $d_2 = 0.25$, $d_3 = 0.50$, $d_4 = 0.75$, and $d_5 = 1.00$. At each dose d_i, the response followed a binomial distribution with parameters N and $P(d_i)$, where N is the number of experimental units observed at each dose d_i.

Based on the historical dose-responses observed by the National Cancer Institute's bioassay program, Portier (1982) concluded that, in practical problems, the values of P(0) and P(1) lie in the following intervals:

$$0.001 \leq P(0) \leq 0.30 \qquad \text{and} \qquad 0.15 \leq P(1) \leq 0.90.$$

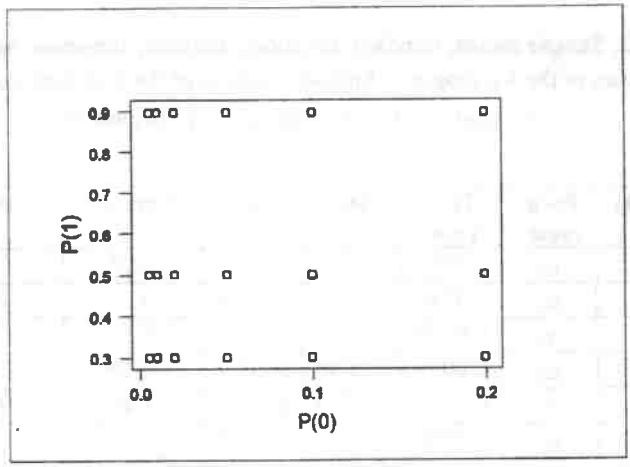
To define the model in (4) uniquely, we need to choose three dose-response points. We considered three doses, d = 0, d = 0.5 and d = 1 = the maximum tolerated dose. Furthermore, we set the response at d = 0.5 as follows: $P(0.5) = 0.5\ P(1)$ whenever $P(0) \leq 0.05$, and $P(0.5) = 0.5\ (P(0) + P(1))$ for $P(0) > 0.05$. To make the results of the study widely applicable, we selected the values of α_0, α_1, and α_2, or equivalently, P(0) and P(1), as listed in Table 1 and displayed in Figure 1.

To determine the asymptotic properties and distribution of the MSAE estimators of the parameters of the model, we used N = 10 000. For each model, we generated and estimated 1800 dose-response curves using the MSAE criterion. For the Monte Carlo distributions of α_0, α_1, and α_2 we computed the mean, the standard deviation, the kurtosis, the skewness and tested their normality using the Kolmogorov-Smirnov test statistic and used critical values of Lilliefors (1967).

Table 1: Values of P(0), P(1) and the parameters α_0, α_1, and α_2 used in the study for the linear-quadratic dose-response model

P(0)	P(1)	α_0	α_1	α_2
0.005	0.30	0.0050	0.2784	0.0733
0.005	0.50	0.0050	0.4425	0.2456
0.005	0.90	0.0050	0.0737	2.2238
0.010	0.30	0.0101	0.0833	0.2634
0.010	0.50	0.0101	0.4276	0.2556
0.010	0.90	0.0101	0.0585	2.2340
0.020	0.30	0.0202	0.2328	0.1037
0.020	0.50	0.0202	0.3970	0.2760
0.020	0.90	0.0202	0.0282	2.2542
0.050	0.30	0.0513	0.1395	0.1659
0.050	0.50	0.0513	0.3037	0.3382
0.050	0.90	0.0513	0.3161	1.9352
0.100	0.30	0.1054	0.2305	0.0208
0.100	0.50	0.1054	0.4282	0.1596
0.100	0.90	0.1054	0.1539	2.0433
0.200	0.30	0.2231	0.1246	0.0089
0.200	0.50	0.2231	0.2393	0.2307
0.200	0.90	0.2231	0.2220	1.8574

Figure 1. Values of P(0) and P(1) used in the study



In the second stage of the study, we proceeded as follows: over the region where the estimators follow normal distribution, we used N = 15, 20, 30, ..., 500 in steps of size 10. For given values of (P(0), P(1)) and N, we generated 1800 dose-response curves using the MSAE criterion to estimate the parameters of the model. For each set of 1800 dose-response curves, we computed the following: if the mean values of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ were within 15 percent of the true values of α_0, α_1, and α_2 , we compared the percentiles (2.5, 5, 95, and 97.5) of the Monte Carlo distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ with those of the normal distributions with means and variances equal to the means and variances of the Monte Carlo distributions; if the percentiles were similar, we checked if the variance of the estimators are close to that given by the diagonal elements of the estimated variance-covariance matrix of the estimators; for more details see Section 4.

Over the region where the asymptotic distribution of $\hat{\alpha}_0$, $\hat{\alpha}_1$, or $\hat{\alpha}_2$ is not normal, we first compared the percentiles (2.5, 5, 95, and 97.5) of the asymptotic distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ and those of the normal distributions with means and variances equal to the observed means and variances of the asymptotic distributions to see if their tails behave alike. If the tails for the two distributions were similar, then we tried to find the smallest sample size at which the normal distribution may be used to draw inferences about the parameters of the model.

3. RESULTS AND DISCUSSION

For selected values of the parameters, the mean, the standard deviation, the kurtosis, the skewness of the Monte Carlo distributions, and the value of the Kolmogorov-Smirnov test statistic for normality are displayed in Table 2. We used the critical values of Lilliefors(1967) to test normality. From Table 2, we observe that the behavior of the MSAE estimators for the linear-quadratic dose-response model is not as well defined as

for the linear dose-response model. For example, the distribution of $\hat{\alpha}_0$ may not be normal even for large values of P(0) or P(1).

Table 2: Sample means, standard deviations, kurtosis, skewness, and observed values of the Kolmogorov-Smirnov statistic of the distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ for selected value of P(0) and P(1).

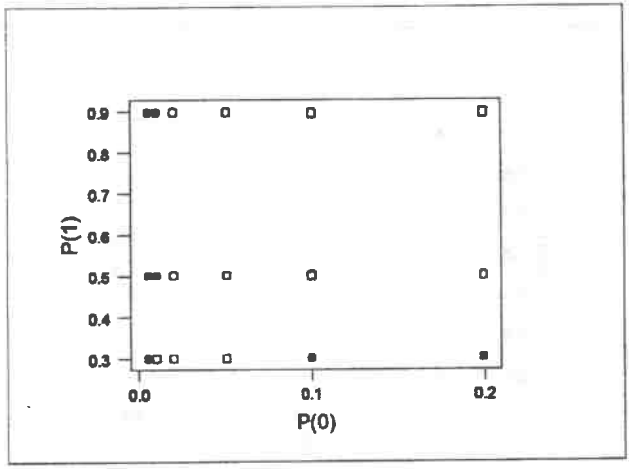
P(0)	P(1)	Para-meter	True Value	Mean	Std. dev.	Kurtosis	Skewness	K-S(*)
0.005	0.30	α_0	0.0050	0.0050	0.0007	0.02	0.15	0.034
		α_1	0.2784	0.2785	0.0154	0.32	-0.07	0.017
		α_2	0.0733	0.0733	0.0195	0.30	0.11	0.016
0.005	0.90	α_0	0.0050	0.0050	0.0007	-0.06	0.11	0.037
		α_1	0.0737	0.0739	0.0275	3.46	0.41	0.019
		α_2	2.2238	2.2237	0.0435	1.38	-0.28	0.013
0.010	0.30	α_0	0.0101	0.0100	0.0010	0.20	0.00	0.013
		α_1	0.0833	0.0837	0.0137	0.24	0.06	0.021
		α_2	0.2684	0.2690	0.0180	0.12	-0.04	0.018
0.02	0.30	α_0	0.0202	0.0202	0.0014	-0.04	0.07	0.016
		α_1	0.2328	0.2323	0.0157	-0.03	-0.06	0.018
		α_2	0.1037	0.1044	0.0191	0.04	0.03	0.008
0.02	0.90	α_0	0.0202	0.0202	0.0014	0.04	0.02	0.021
		α_1	0.0282	0.0312	0.0265	22.12	2.26	0.120
		α_2	2.2542	2.2499	0.0469	7.69	-1.17	0.040
0.20	0.30	α_0	0.2231	0.1933	0.0507	2.37	-1.68	0.290
		α_1	0.1246	0.1770	0.1205	9.27	2.53	0.244
		α_2	0.0089	0.0163	0.0192	1.40	1.24	0.198
0.20	0.90	α_0	0.2231	0.2233	0.0060	0.02	0.09	0.014
		α_1	0.2220	0.2210	0.0462	0.84	-0.15	0.012
		α_2	1.8574	1.8592	0.0672	0.46	0.14	0.018

(*) 1% critical value = 0.028.

Based on the results of the Monte Carlo study, we may conclude the following:

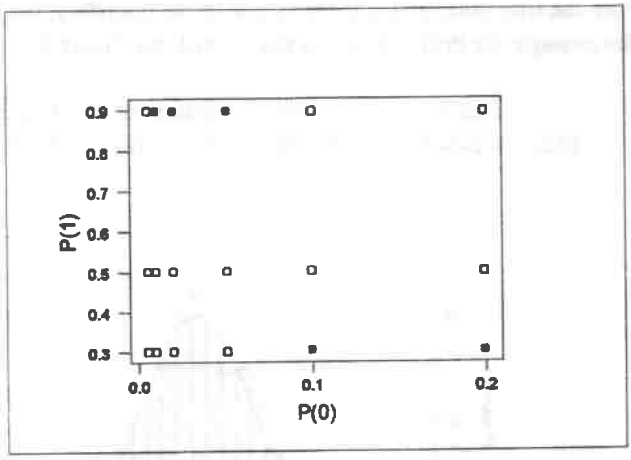
- The MSAE estimators $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ are not always unbiased, for example, see the results corresponding to P(0) = 0.20 and P(1) = 0.30, Table 2. Estimators are unbiased only in the region where the distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ are normal.
- The regions, over which the asymptotic distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ are normal, are displayed in Figures 2, 3, and 4.

Figure 2: Region where the distribution of $\hat{\alpha}_0$ is asymptotically normal



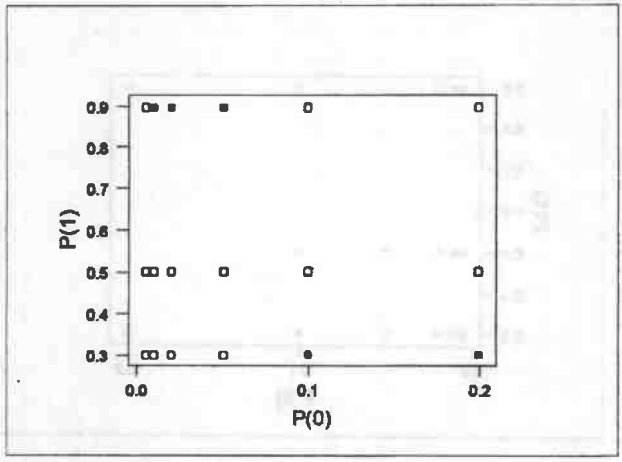
o : normal

Figure 3: Region where the distribution of $\hat{\alpha}_1$ is asymptotically normal



o : normal

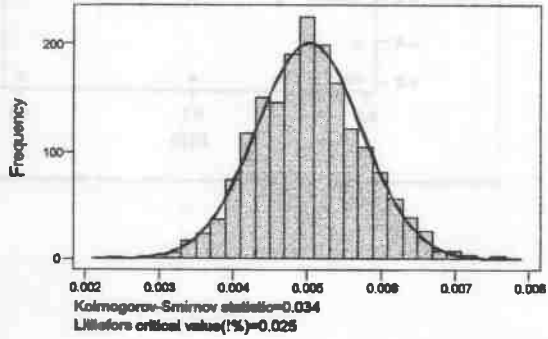
Figure 4: Region where the distribution of $\hat{\alpha}_2$ is asymptotically normal



o : normal

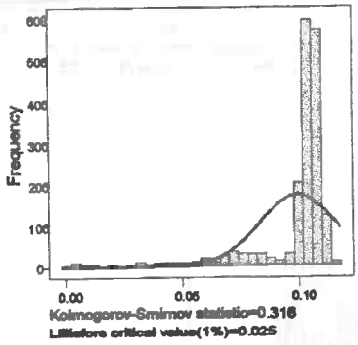
- The estimators do not follow normal distribution whenever at least one of the parameters has a small value.
  - When the true value of α_0 is very close to the boundary, the distribution of $\hat{\alpha}_0$ (for example for P(0) = 0.005) is not normal, see Figure 5.

Figure 5: Asymptotic distribution of $\hat{\alpha}_0$ .True model :
$P(d) = 1-\exp(-0.005-0.2784d-0.0733d^2)$, (P(0) = 0.005, P(1) = 0.30).

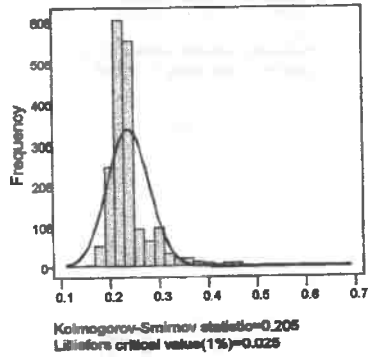


- When α_1 or α_2 are close to the boundary, the responses obtained from the models tend to fit a linear ($\alpha_1 = 0$) or a quadratic ($\alpha_2 = 0$) model; that is, α_1 or α_2 are incorrectly estimated as zero. This may be because $\alpha_1 + \alpha_2$ are related to P(1) as shown in (5b) resulting in a non-identifiability problem. This fact substantially affects the other estimates and can result in nonnormal distributions, see Figures 6 and 7.

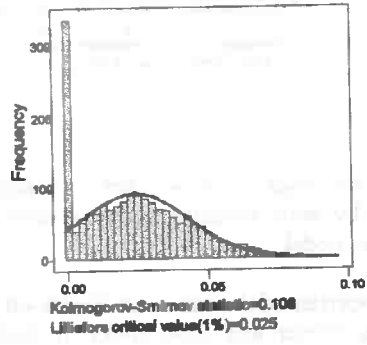
Figure 6: Asymptotic distribution of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$. True model : $P(d) = 1 - \exp(-0.1054 - 0.2305d - 0.0208d^2)$, (P(0) = 0.10, P(1)=0.30).



$\hat{\alpha}_0$

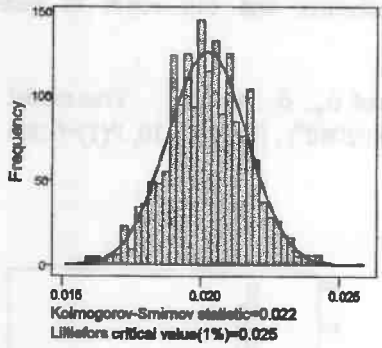


$\hat{\alpha}_1$

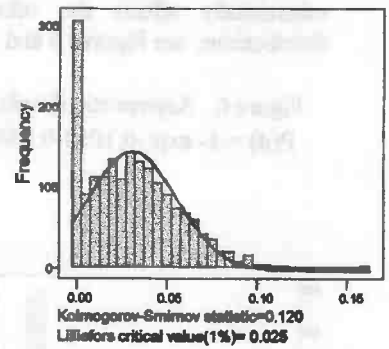


$\hat{\alpha}_2$

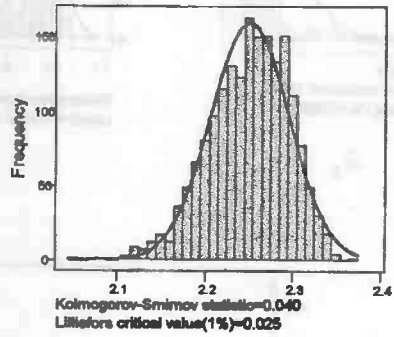
Figure 7: Figure - Asymptotic distribution of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$. True model : P(d) = 1-exp(-0.0202-0.0282d-2.2542d^2)



$\hat{\alpha}_0$



$\hat{\alpha}_1$



$\hat{\alpha}_2$

From Figures 6 and 7, we observe that whichever parameter, α_0 or α_1, is very small, it is more often estimated by zero resulting in incorrectly fitting the model as linear or quadratic dose-response model.

In their study of the properties of the maximum likelihood estimator of the safe-dose in the linear quadratic model, Poitier and Hoel (1983, p. 902), observed similar results and stated, " It is possible to consider the linear-quadratic model as falling between the linear and quadratic models. Responses obtained from this underlying model will tend towards both linear and quadratic with high probability and will very seldom fit a linear-quadratic

model. Thus, the frequency of fitting an incorrect model increases, and ranges from 5% to 95%, that is, $.05 < \text{pr}(\hat{\alpha}_1 = 0 \text{ or } \hat{\alpha}_2 = 0) < .95$."

For the points where the Monte Carlo distributions of at least one of the estimators $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$ are not normal, we verified if the tails of the Monte Carlo distributions converge to the tails of a normal distribution. To do so, we computed the 2.5, 5, 95, and 97.5 percentiles of the Monte Carlo and normal distributions. The results are given in Table 3.

Table 3: The observed percentiles of the normal and Monte Carlo distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$.

				Percentile			
P(0)	P(1)		Method	2.5	5	95	97.5
0.005	0.30	$\hat{\alpha}_0$	Monte Carlo	0.0037	0.0039	0.0063	0.0065
			Normal	0.0036	0.0038	0.0062	0.0064
		$\hat{\alpha}_1$	Monte Carlo	0.2488	0.2534	0.3039	0.3096
			Normal	0.2484	0.2533	0.3037	0.3086
		$\hat{\alpha}_2$	Monte Carlo	0.0347	0.0415	0.1048	0.1120
			Normal	0.0349	0.0410	0.1052	0.1113
0.005	0.50	$\hat{\alpha}_0$	Monte Carlo	0.0037	0.0039	0.0062	0.0065
			Normal	0.0037	0.0039	0.0063	0.0065
		$\hat{\alpha}_1$	Monte Carlo	0.4000	0.4075	0.4775	0.4836
			Normal	0.4010	0.4077	0.4772	0.4838
		$\hat{\alpha}_2$	Monte Carlo	0.1924	0.2016	0.2922	0.3009
			Normal	0.1918	0.2005	0.2914	0.3001
0.005	0.90	$\hat{\alpha}_0$	Monte Carlo	0.0037	0.0039	0.0062	0.0064
			Normal	0.0037	0.0039	0.0062	0.0064
		$\hat{\alpha}_1$	Monte Carlo	0.0201	0.0293	0.1173	0.1267
			Normal	0.0200	0.0286	0.1191	0.1277
		$\hat{\alpha}_2$	Monte Carlo	2.1280	2.1463	2.3048	2.3209
			Normal	2.1286	2.1439	2.3035	2.3189
0.010	0.50	$\hat{\alpha}_0$	Monte Carlo	0.0080	0.0084	0.0119	0.0123
			Normal	0.0080	0.0084	0.0119	0.0122
		$\hat{\alpha}_1$	Monte Carlo	0.3874	0.3937	0.4616	0.4708
			Normal	0.3866	0.3932	0.4621	0.4687
		$\hat{\alpha}_2$	Monte Carlo	0.1986	0.2107	0.2994	0.3093
			Normal	0.2105	0.2101	0.3003	0.3089

Table 3 (continued): The observed percentiles of the normal and Monte Carlo distributions of $\hat{\alpha}_0$, $\hat{\alpha}_1$, and $\hat{\alpha}_2$.

				Percentile			
P(0)	P(1)		Method	2.5	5	95	97.5
0.010	0.90	$\hat{\alpha}_0$	Monte Carlo	0.0080	0.0084	0.0118	0.0121
			Normal	0.0081	0.0084	0.0117	0.0120
		$\hat{\alpha}_1$	Monte Carlo	0.0056	0.0155	0.1063	0.1161
			Normal	0.0051	0.0139	0.1054	0.1141
		$\hat{\alpha}_2$	Monte Carlo	2.1318	2.1542	2.3120	2.3261
			Normal	2.1374	2.1528	2.1333	2.3287
0.020	0.90	$\hat{\alpha}_0$	Monte Carlo	0.0174	0.0179	0.0226	0.0231
			Normal	0.0174	0.0179	0.0226	0.0230
		$\hat{\alpha}_1$	Monte Carlo	0.0000	0.0000	0.0755	0.0843
			Normal	-0.2070	-0.0123	0.0747	0.0830
		$\hat{\alpha}_2$	Monte Carlo	2.1522	2.1721	2.3162	2.3274
			Normal	2.1580	2.1728	2.3270	2.3418
0.100	0.30	$\hat{\alpha}_0$	Monte Carlo	0.0490	0.0663	0.1106	0.1120
			Normal	0.0675	0.0727	0.1268	0.1320
		$\hat{\alpha}_1$	Monte Carlo	0.1887	0.1949	0.3138	0.3543
			Normal	0.1549	0.1683	0.3084	0.3218
		$\hat{\alpha}_2$	Monte Carlo	0.0000	0.0000	0.0597	0.0671
			Normal	-0.0140	-0.0079	0.0558	0.0620
0.200	0.30	$\hat{\alpha}_0$	Monte Carlo	0.0425	0.0839	0.2311	0.2327
			Normal	0.0940	0.1099	0.2766	0.2926
		$\hat{\alpha}_1$	Monte Carlo	0.0712	0.0803	0.4140	0.5147
			Normal	-0.0591	-0.0211	0.3752	0.4131
		$\hat{\alpha}_2$	Monte Carlo	0.0000	0.0000	0.0535	0.0626
			Normal	-0.0214	-0.0153	0.0478	0.0539

From Table 3, it is clear that the percentiles of the Monte Carlo distribution converge to the percentiles of the normal distribution except for (P(0), P(1)) equal to (0.02, 0.90), (0.10, 0.30), and (0.20, 0.30). Even for these points, the 95 and 97.5 percentiles for the Monte Carlo and the normal distributions are similar; the discrepancy exists only at the 2.5 and 5.0 percentiles. Because the parameters can not be negative, if the negative values are replaced by zero, we observe that the differences remains only for the 2.5 and 5.0 percentiles for $\hat{\alpha}_0$ and $\hat{\alpha}_1$ at (P(0), P(1)) equal to (0.20, 0.30).

For the linear-quadratic dose-response model, it may not be advisable to use normal distribution to draw statistical inferences about the parameters of the model as it requires more than 500 observations per dose before the tails of the asymptotic and normal distributions behave like. The use of normal distribution to draw statistical inferences

about the parameters of the linear-quadratic dose-response model for small sample sizes may lead to wrong conclusions. Therefore, it seems reasonable to use bootstrap methods to construct confidence intervals and test hypotheses about the parameters, André (1989).

4. ASYMPTOTIC VARIANCE

André (1989) has shown that model (4) can be approximated by a linear model and the errors from (4) may be written as:

$$| e_i | \cong | z_i(lnz_i + \alpha_0 + \alpha_1 d_i + \alpha_2 d_i^2)| \qquad (6)$$

where $z_i = 1 - y_i$, $i = 1, 2, \ldots, n$. Let

$$\frac{|e_i|\sqrt{N}}{\sqrt{y_i(1-y_i)}} \cong \frac{\sqrt{N}}{\sqrt{y_i(1-y_i)}} |z_i(\ln z_i + \alpha_0 + \alpha_1 d_i + \alpha_2 d_i^2)| \equiv |e_i^*|. \qquad (7)$$

Observe that e_i^*'s are the errors of a linear model.

Now, we minimize:

$$\sum_{i=1}^{n} |e_i^*| = \sum_{i=1}^{n} |w_i(\ln z_i + \alpha_0 + \alpha_1 d_i + \alpha_2 d_i^2)|, \qquad (8)$$

where $w_i = \dfrac{\sqrt{N(1-y_i)}}{\sqrt{y_i}}$.

In the region where the MSAE estimators have asymptotic normal distribution, an approximate expression for the variance-covariance matrix is:

$$Var(\hat{\alpha}) = \tau^2 (X' X)^{-1}, \qquad (9)$$

where τ^2/n is the variance of the median of the sample of size n from the error distribution, and

$$X = \begin{bmatrix} w_1 & w_1 d_1 & w_1 d_1^2 \\ w_2 & w_2 d_2 & w_2 d_2^2 \\ w_3 & w_3 d_3 & w_3 d_3^2 \\ w_4 & w_4 d_4 & w_4 d_4^2 \\ w_5 & w_5 d_5 & w_5 d_5^2 \end{bmatrix}.$$

One may use any consistent estimator of τ to estimate the variance covariance of $\hat{\alpha}$. Let, $\hat{e}_1, \hat{e}_2, \ldots, \hat{e}_n$ be the residuals from the MSAE fit of model (4) and $\hat{e}^*_{(1)}, \hat{e}^*_{(2)}, \ldots, \hat{e}^*_{(n^*)}$

denote the non-zero residuals from (8) arranged in an ascending order, where n^* is the number of non-zero residuals. Birkes and Dodge (1993) and McKean and Schrader (1984) recommend the estimator:

$$\hat{\tau} = \sqrt{n^*}(\hat{e}^*_{(n^*-m+1)} - \hat{e}^*_{(m)})/4.$$

where $m = (n^* + 1)/2 - \sqrt{n^*}$.

5. SUMMARY

For the linear-quadratic dose-response model, the results are not as encouraging as for the linear dose-response model. The model is incorrectly estimated for quite a few values of the parameters. The asymptotic distribution of the estimators is not normal if any of the parameters is close to the boundary value. Furthermore, it needs a sample size larger than 500 at each dose before the normal distribution may be used to draw statistical inference about the parameters of the model. Therefore, for small sample sizes, a more practical procedure to draw inferences about the parameters of the model would be to use bootstrap methods, André (1989).

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