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Generalized Confidence Intervals for Low-dose Risk assessment with Nonquantal Data

Dewi Tanasia Saputra[a], **Jianan Peng**[*a] **and Jian Xiong**[b]

[a]*Department of Mathematics and Statistics,*
Acadia University, Wolfville, NS, B4P 2R6, Canada.

[b]*Department of Statistics, School of Economics and Statistics,*
Guangzhou University, 510006, China.

Abstract

Risk assessment studies where human, animal or ecological data are used to set safe low dose levels of a toxic agent are challenging as study information is limited to high dose levels of the agent. However, interest often exists in the low-risk responses associated with doses closer to zero and careful statistical studies are needed to make appropriate inference on the low-dose effects from the high-dose data. Piegorsch et al. (Journal of Biopharmaceutical Statistics Vol 15: 17-31) discussed several interval estimates for low-dose risk assessment. In this paper, we propose generalized confidence intervals for low-dose risk assessment. The new method is very competitive with the methods in the literature.

Key words and phrases: Benchmark dose; Environmental risk assessment; Generalized confidence interval.

AMS 2000 Subject Classificaitons: *Primary* **62J10** , *Secondary* **62J25**.

1. INTRODUCTION

An important goal in quantitative risk assessment is characterization of detrimental or adverse responses after exposure to biological, chemical, environmental, or other hazardous agents. To assess the potential risk of exposures to such an agent,

[*]Corresponding author (Email ID: jianan.peng@acadiau.ca)

experiments are often conducted on animals in the laboratory where the exposure levels of the agent are administered at a relatively high dose, although the interest typically lies in the determination of risk at a lower dose.This is due to more animals are needed to observe the effects of the agent at a lower dose. As a result, the low-dose inferences must be extrapolated from the results obtained at high-dose levels. For illustration, consider the following example in Piegorsch et al. (2005a).

1.1. Aconiazide toxicity:

Beland et al. (1995) reported the antituberculosis drug Aconiazide (CASRN 13410-86-1) study. The study involved data collection over a 6-month period to assess the drug's systemic toxicity in male Fischer 344 rats that received the drug daily via gavage. The continuous outcome variable recorded was the animals' body weight change (gain or loss in g) at the end of the study. There were four dose levels: 0, 100, 200, and 400 mg/kg. The response over these doses exhibited a decreasing pattern, see Table 1. Piegorsch et al. (2005a) analyzed this data set as well.

Table 1: Body weight changes (in g) of F344 rats after exposure to the antituberculosis drug Aconiazide (CASRN 13410-86-1)

Exposure dose (mg/kg)			
0	**100**	**200**	**400**
366.00	342.80	302.60	286.70
326.60	342.20	328.90	237.40
355.00	306.10	284.60	246.00
353.80	338.10	319.30	265.90
354.40	335.80	298.70	265.50
349.80	335.40	305.30	253.40
378.90	304.50	340.50	262.50
378.20	339.80	254.70	272.80
342.80	336.10	328.40	267.70
383.60	323.20	279.90	259.60
345.90	359.00	279.30	277.40
376.80	349.00	324.40	255.50
360.80	335.10	342.00	-
Sample means			
360.56	333.49	308.23	260.97

As Piegorsch et al. (2005a) pointed out that Aconiazide usually would be administered to humanns at mg/kg levels below the higher doses used in this toxicity study. Therefore, one of the scientific concerns is to understand the drug's (mammalian) toxicity at low doses. It is of interest to characterize how the risk changes over changing doses and assessing at what low dose levels, if any, the toxicity can be kept to an acceptable standard to human or mammals.

Piegorsch et al. (2005a) developed five methods to obtain $100(1-\alpha)\%$ upper bounds on additional risk function that can be simultaneously used for a range of x-values which are positive by the nature of dose levels. Their five methods can then be used to calculate simultaneous $100(1-\alpha)\%$ lower confidence bounds on any number of benchmark doses-even post hoc- for use as points of departure in a qunatitative risk assessment (Piegorsch et al. (2005a)). These five methods were listed in Table 1 of their paper. They were all based on asymptotic argument. They recommended Akahira's (1995) Cornish-Fisher expansion based on their Monto Carlo studies. In this paper, we propose to use generalized confidence interval to make simultaneous inference in risk analysis for normal data.

The rest of the article is organized as follows. The statistical model and the confidence band methodology for risk estimation for normal data are reviewed in Section 2. Our new confidence interval estimate based generalized confidence interval is described in Section 3. Monte Carlo evaluations on the coverage characteristics of the methods are given in Section 4. The new proposed method is illustrated with a real data in Section 5. A brief discussion is given in Section 6.

2. RISK ESTIMATION FOR NORMAL DATA

Following Piegorsch et al. (2005a), we assume that the observed data are continuous, reflecting the adverse effect of some toxic exposure. Let $Y(x_i) = \mu(x_i) + e_i$ with independent $e_i \sim N(0, \sigma^2)$, $i = 1, \ldots, n$, and $\mu(x_i) = \beta_0 + \beta_1 x_i$, where the x_is are the recorded dose values and σ is unkown. Denote $S_{xx} = \sum_{i=1}^{n}(x_i - \bar{x})^2$. Following the literature, the risk function is defined as $R(x) = P(Y(x) \leq \mu(0) - \delta\sigma)$, where $\delta > 0$ is a constant value such as 2 or 3 to tune the risk for specific applications

Under the normal model above, like Piegorsch et al. (2005a), we have the additional risk funciton $R_A(x) = \Phi\{-\gamma_1 x - \delta\} - \Phi(-\delta)$ to characterize exposure risk, where $\gamma_1 = \beta_1/\sigma$ (Chen and Gaylor, 1992) and $\Phi(\cdot)$ is the cumulative distribution function of the standard normal distribution. This risk function is often used in regulatory efforts to establish a low dose or low exposure level that is needed to generate a specific R_A in the target population after exposure to the hazardous agent i.e., given a risk

benchmark BMR $\in (0,1)$, the estimated dose–response model is inverted to find the level of x that produces this bench–mark risk: set $R_A(x)$ =BMR and solve for x. The resulting value of x is known in a risk assessment as the *benchmark dose* (BMD) (Piegorsch et al. (2005a)). We use maximum likelihood method to estimate the parameter $\gamma_1 = \beta_1/\sigma$. For the simple linear model, the maximum likelihood estimator (MLE) of β_1 is $\hat{\beta}_1 = \sum_{i=1}^{n}(x_i - \bar{x})Y_i/S_{xx}$, the MLE for σ is the root mean squared error S, where $S^2 = \frac{\sum_{i=1}^{n}(Y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i)^2}{n-2}, \hat{\beta}_0 = \bar{Y} - \hat{\beta}_1\bar{x}$. The MLE of $\gamma_1 = \beta_1/\sigma$ is $\hat{\gamma_1} = (\hat{\beta}_1/S)n/(n-2)^{1/2}$. Since $\hat{\gamma_1}$ is biased, following Piegorsch et al. (2005a), we use the unbiased estimator $g_1 = \xi_n\hat{\beta}_1/S$, where

$$\xi_n = \frac{\Gamma\{(n-2)/2\}}{\Gamma\{(n-3)/2\}}\sqrt{\frac{2}{n-2}}$$

and $\Gamma(.)$ is the gamma function and we need $n \geq 4$. Therefore, the MLE of $R_A(x)$ is $\hat{R_A(x)} = \Phi(-g_1x - \delta) - \Phi(-\delta)$.

To estimate a benchmark dose at a given benchmark risk, 0¡BMR¡1, we set $\hat{R}_A(x)$=BMR and solve for x. The smallest positive real root of this equation is taken as $\widehat{\mathrm{BMD}_{100BMR}}$.

2.1. Lower Bounds on γ_1

Construction of upper bounds on the additional risk function $R_A(x)$ is equivalent to obtaining lower bounds on γ_1. This is easy to verify. Suppose we have a lower bound $G_{L,\alpha}$ such that $P(G_{L,\alpha} < \gamma_1) = 1 - \alpha$. Therefore, $P(G_{L,\alpha} < \gamma_1) = P(-G_{L,\alpha} > -\gamma_1) = P(-\gamma_1 < -G_{L,\alpha}) = P(-\gamma_1 x < -G_{L,\alpha}x, \forall x > 0) = P(-\gamma_1 x - \delta < -G_{L,\alpha}x - \delta, \forall x > 0) = P(\Phi(-\gamma_1 x - \delta) < \Phi(-G_{L,\alpha}x - \delta), \forall x > 0) = P(\Phi(-\gamma_1 x - \delta) - \Phi(-\delta) < \Phi(-G_{L,\alpha}x - \delta) - \Phi(-\delta), \forall x > 0) = P(R_A(x) < \Phi(-G_{L,\alpha}x - \delta) - \Phi(-\delta), \forall x > 0) = 1 - \alpha$. Hence, given the $1-\alpha$ lower bound $G_{L,\alpha}$ on γ_1, the resulting simultaneous $1-\alpha$ upper bound on $R_A(x)$ is $\Phi(-G_{L,\alpha}x - \delta) - \Phi(-\delta), \forall x > 0)$. There are several methods to obtain the lower bound on γ_1 in the literature.

- The exact confidence lower bound on γ_1 is computationally prohibitive.
- Piegorsch et al. (2005a) discussed five confidence lower bounds for γ_1 based on asymptotic approximation. They concluded that Akahira's Cornish-Fisher expansion method is the best. Here we present three of the five methods in their Table 1. We will compare these three methods with the new method proposed in the paper in the simulation studies in Section 4.
- Asymptotic standard normal with $G_{1,\alpha} = \frac{g_1}{\kappa_n} - \frac{Z_\alpha}{\sqrt{S_{xx}}}$.

- Vangel (1996)'s $\chi^2(n-2)$ approximation with $G_{2,\alpha} = -\sqrt{\frac{\chi^2_\alpha(n-2)}{n-2}\left(\frac{\hat{\beta}^2}{S^2}+\theta\right)-1}$, where $\theta = (n-2)\{1+[2/\chi^2_\alpha(n-2)]\}/(n-1)$
- Akahira's Cornish-Fisher expansion with

$$\begin{aligned} G_{3,\alpha} &= S_{xx}^{-1/2}\Bigg[\lambda_n T_1 - Z_\alpha\sqrt{1+T_1^2(1-\lambda_n^2)} \\ &\quad + \frac{T_1^3(Z_\alpha^2-1)}{24(n-2)^2(1+T_1^2(1-\lambda_n^2))}\left(1+\frac{1}{4(n-2)}\right)\Bigg], \end{aligned}$$

where $T_1 = g_1 S_{xx}^{1/2}/\xi_n$ and $\lambda_n = \frac{\Gamma(\frac{n-1}{2})}{\Gamma(\frac{n-2}{2})}\sqrt{\frac{2}{n-2}}$.

2.2. Lower bound on BMD

Given a value for the desired benchmark risk (BMR), we find the corresponding BMD_{100BMR} by setting the estimated $R_A(x)$ function equal to BMR and solving for x. We have

$$\hat{BMD}_{100BMR} = -\frac{\delta + \Phi^{-1}(BMR + \Phi(-\delta))}{g_1}. \tag{2.1}$$

Similarly, suppose we find a simultaneous upper band on $R_A(x)$ with $P(R_A(x) < \Phi(-G_{L,\alpha}x-\delta)-\Phi(-\delta)), \forall x>0) = 1-\alpha$, the simultaneous BMDLs for BMD can be obtained by solving the equation $\Phi(-G_{L,\alpha}x-\delta)-\Phi(-\delta)) = BMR$, then

$$\hat{BMDL}_{100BMR} = -\frac{\delta + \Phi^{-1}(BMR + \Phi(-\delta))}{G_{L,\alpha}} \tag{2.2}$$

Note that these $1-\alpha$ lower bounds are simultaneous for all possible BMRs.

3. LOWER BOUNDS ON γ_1 BASED ON GENERALIZED CONFIDENCE INTERVALS

Weerahan (1993,1995) introduced the concept of generalized confidence interval, which is used to construct an interval for the scalar parameter where standard methods may not be applicable. Generalized confidence intervals have been used in many areas in statistics but not yet in risk assessment, to the best of our knowledge. In this section we propose a new method for lower bounds on γ_1 based on generalized confidence intervals.

Consider a population with the cdf $F(Y|\lambda)$, where $\lambda = (\theta, \delta)$ are the unknown parameters, θ is the parameter of interest, and δ is the nuisance parameter. The

confidence interval for θ based on the observed values Y is denoted by

$$P[A(Y) \leq \theta \leq B(Y)] = 1 - \alpha$$

where $A(Y)$ and $B(Y)$ are a statistics free of the parameter of interest θ. Since $A(Y)$ and $B(Y)$ might have the nuisance parameter in them, it is hard to formulate a general formula that can satisfy all the possible range for the nuisance parameter.

To do this, we will define a generalized pivotal quantity. Generalized pivotal quantity is a quantity $R = r(Y; y, \lambda)$ with a distribution free of the unknown parameters, and the observed values $r_{obs} = r(y; y, \lambda)$ doesn't depend on the nuisance parameter δ. We would want our function $A(Y)$ and $B(Y)$ in the equation above to be a generalized pivotal quantity to construct the generalized confidence intervals.

Denote $U = \dfrac{\sum_{i=1}^{n}(Y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i)^2}{\sigma^2} \sim \chi^2_{n-2}$. From $Z = \frac{\hat{\beta}_1 - \beta_1}{\frac{\sigma}{\sqrt{S_{xx}}}} \sim N(0,1)$, we define $\beta_1 = \hat{\beta}_1 - \frac{Z\sigma}{\sqrt{S_{xx}}}$.

Rewrite the equation above in terms of R notation:

$$R_{\beta_1} = \hat{\beta}_1 - Z\frac{\sqrt{R_{\sigma^2}}}{\sqrt{S_{xx}}}, \tag{3.3}$$

where $R_{\sigma^2} = \dfrac{\sum_{i=1}^{n}(Y_i - \hat{\beta}_0 - \hat{\beta}_1 x_i)^2}{U}$.

Since the parameter of interest used in the function $R_A(x)$ is γ_1 with the unbiased estimator $g_1 = \xi_n \hat{\beta}_1 / S$,

$$R_{\gamma_1} = \frac{R_{\beta_1}\xi_n}{\sqrt{R_{\sigma^2}}}. \tag{3.4}$$

We repeat the process N times to obtain N (say $N = 10000$) values R_{γ_1}, the $100(1-\alpha)\%$ lower bound for γ_1 is the $100(1-\alpha)$th percentile of R_{γ_1}'s.

4. SIMULATION STUDIES

All the methods for constructing confidence bands for $R_A(x)$ or finding BMDL in Piegorsch et al. (2005a) are based on asymptotic approximation. The simultaneous coverage is expected to be approximately correct with $1 - \alpha$. Piegorsch et al. (2005a) recommended Akahira's (1995) Cornish-Fisher expansion method for banding R_A or for finding BMDL through simulation studies. Small sample sizes however are not uncommon in practice. It is often of interest to evaluate the small sample coverage

characteristics of the methods via Monte Carlo studies. In this section, we present some simulation results to compare the empirical simultaneous coverage probabilities for the Akahira's (1995) method and the new method. We basically follow the simulation design in Piegorsch et al. (2005a). We considered two models used in previous studies of low-dose risk estimation. Model 1 was taken from simulaiton study by Chen and Gaylor (1992) with the parameters $\beta_0 = 16.25, \beta_1 = -0.001$ and $\sigma = 1.0$. Four dose levels were 0, 500, 1000, and 2000. The number of equal replications was taken so that the total sample size ranged over n=20, 40, 60, and 100. Model 2 was from a simulation study conducted by West and Kodell (1999) with $\beta_0 = 3.0, \beta_1 = -1.0$, and $n = 25, 50, 100, 150, 200$; Dose level x will be equally replicated with $0, 1, 2, 3, 4$ for each n.

Let $\alpha = 0.05$. For each parameter configuration chosen in the study we generated 10000 and four dose levels We used R version 4.5.0 for the simulation.

The simulation results appear in Table A.2 for Model 1 and Table A.3 for Model 2, respectively. They are the empirical simultaneous coverage on $R_A(x)$. Across both models and for all scenarios considered, both Akahira's (1995) method and the new method provide very close nominal 95% coverage probability and other two methods are either too conservative or below the nominal 95% level. Our conclusions are very similar to Piegorsch et al. (2005a) and we recommend to use either Akahira's (1995) method or the new method.

Table 2: Coverage Probability for Model 1

Method	**n=20**	**n=40**	**n=60**	**n=80**	**n=100**
$G_{1,\alpha}$	0.954	0.926	0.942	0.934	0.939
$G_{2,\alpha}$	1.000	1.000	1.000	1.000	1.000
$G_{3,\alpha}$	0.956	0.934	0.950	0.940	0.950
Proposed	0.953	0.931	0.950	0.938	0.948

Table 3: Coverage Probability for Model 2

Method	**n=25**	**n=50**	**n=100**	**n=150**	**n=200**
$G_{1,\alpha}$	0.907	0.882	0.897	0.912	0.893
$G_{2,\alpha}$	0.994	0.990	0.995	0.994	0.989
$G_{3,\alpha}$	0.951	0.930	0.948	0.964	0.944
Proposed	0.945	0.922	0.946	0.9642	0.943

5. REAL DATA EXAMPLE

We will use the real data example in Section 1 to compare our proposed method using generalized confidence interval with Akahira's method. Recall that the lower bound given by Akahira's method is defined by

$$G_{3,\alpha} = S_{xx}^{-1/2}\left[\lambda_n T_1 - Z_\alpha\sqrt{1+T_1^2(1-\lambda_n^2)} + \frac{T_1^3(Z_\alpha^2-1)}{24(n-2)^2(1+T_1^2(1-\lambda_n^2))}\left(1+\frac{1}{4(n-2)}\right)\right] \tag{5.5}$$

with $\lambda_n = \sqrt{2/(n-2)}\Gamma\left((n-1)/2\right)/\Gamma\left((n-2)/2\right)$, $S_{xx} = \sum_{i=1}^{n}(x_i - \bar{x})^2$ and $T_1 = g_1 S_{xx}^{1/2}/\xi_n$.

Fitting the data to a linear model gives us the coefficients: $\hat{\beta}_0 = 359.19873$, $\hat{\beta}_1 = -0.24802$, $S = \sqrt{MSE} = 18.3993$ and $S_{xx} = 1173455$. We also use $\delta = 3$, $n = 55$, $\nu = 53$, $\alpha = 0.05$ and $\xi_{55} = 0.98577$ in this numerical example. Piegorsch et al. (2005a) had $g_1 = -0.01329$. For the new proposed method GCI, we will generate 100,000 random values of U and Z to get 100,000 values of R_{γ_1} given in Equation (3). Taking the mean of the 100,000 values as our estimated γ_1, we get -0.01336 for g_1 based on GCI. Both methods' estimators for γ_1 are very close to each other.

By using Akahira's method in equation (5),Piegorsch et al. (2005a) calculated their lower bound $G_{3,0.05} = -0.016072$. On the other hand, the 95% lower bound given by our proposed method using GCI is simply the 95th percentile of the 100,000 values of R_{γ_1}, GCI $= -0.016004$. The 95% upper band given by Akahira's method is $\Phi(0.016072x - 3.0) - \Phi(3.0)$, while the upper band given by the proposed method is $\Phi(0.016004x - 3.0) - \Phi(3.0)$. Figure 1 shows the the estimated $R_A(x)$ curve, given by the black solid line, and two upper 95% confidence band given by Akahira's method and the new proposed method, in red and blue dotted line respectively. Note that the blue and red line overlaps; meaning that they provide similar upper band on the estimated additional risk.

Estimating the BMD and BMDL for the two methods, we simply use the formulas in Equation (1) and Equation (2), respectively. In this example, we will consider three levels of BMR; 0.01, 0.05, and 0.01. The results for these specific BMRs can be seen in Table 4. Figure 2 shows the estimated BMD and BMDL for both of the methods. Once again, since both of the line for BMD and BMDL overlaps, that means our method produced similar numbers with Akahira's method. Both Table 4 and Figure 2 indicate both Akahira's method and the new method provide very close numbers for BMD and BMDL for different BMR.

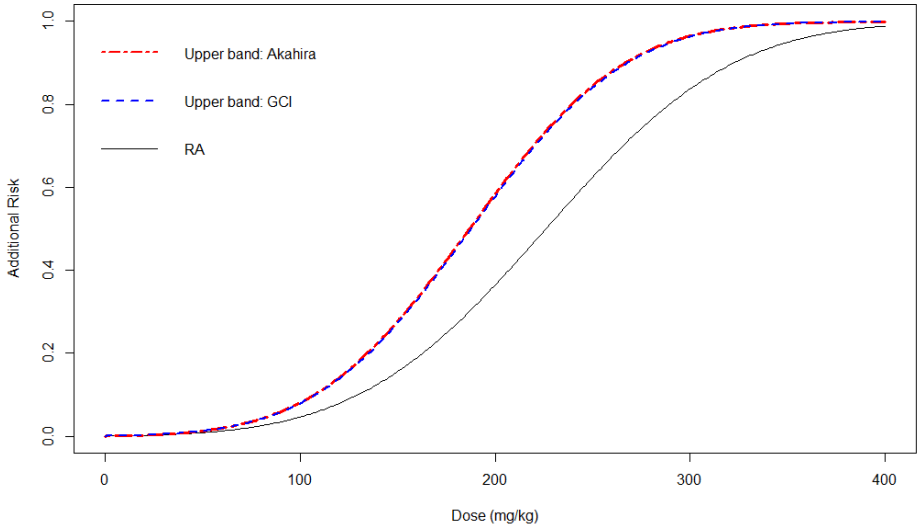

Figure 1: $\hat{R}_A(x)$ function and two 95% upper confidence band

Table 4: BMD and BMDL Results Comparison for the Real Data

	Akahira's Method		**Proposed Method**	
BMR	**BMD**	**BMDL**	**BMD**	**BMDL**
0.01	54.2997	44.8951	54.0184	45.0858
0.05	102.9550	85.1235	102.4217	85.4849
0.10	129.8965	107.3988	129.2236	107.8548

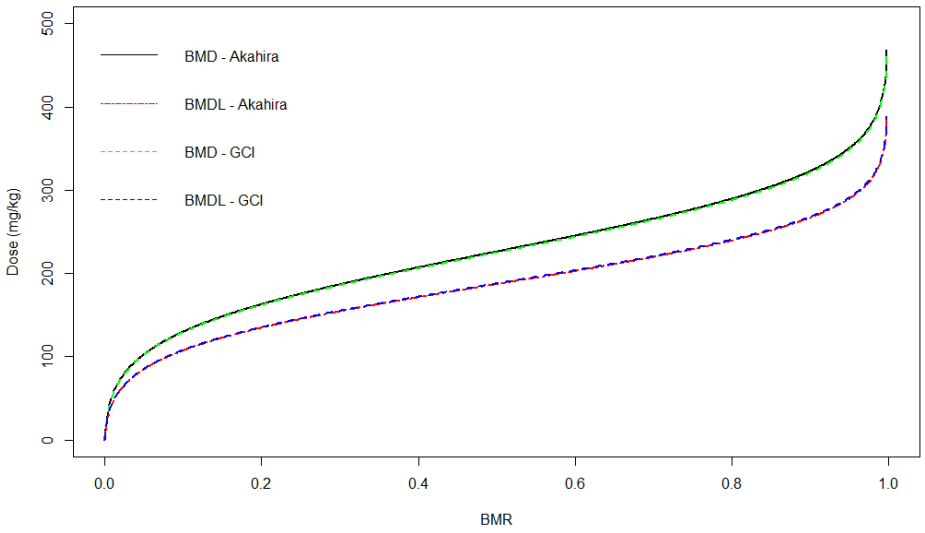

Figure 2: BMD and BMDL by GCI and Akahira

6. DISCUSSION

We have proposed using generalized confidence intervals to construct simultaneous confidence bands for risk assessment, which was not in the literature before. The new method is very competitive with the methods in the literature. Our new method can be applied to other models including the quadratic model in in Piegorsch et al. (2005b), which are mentioned in the section of discussion in Piegorsch et al. (2005a). In this paper we only consider homoscedastic normal data. However, quantal response (binomial) data is very common in low-dose risk assessment, see e.g. Al-Saidy et al. (2003) and Peng et al. (2015). Our new method can be applied to BMDL estimation with quantal response data with proper modification. Of course, some qualifications and caceats discussed in Piegorsch et al. (2005a) are still in order for our new method.

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