

PENNSTATE



Center for **Statistical Ecology** and **Environmental Statistics**

CONTINUOUS DOSE-RESPONSE MODELING AND RISK ANALYSIS
WITH THE GAMMA AND RECIPROCAL GAMMA DISTRIBUTIONS

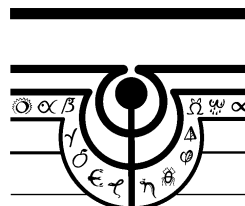
by Senin Banga, G. P. Patil, and C. Taillie

Center for Statistical Ecology and Environmental Statistics
Department of Statistics
The Pennsylvania State University
University Park, PA 16802

EPA Project Officer: Chris Saint

Prepared with partial support from the Office of Research and Development, United States Environmental Protection Agency, Washington, DC under a Cooperative Agreement Number R-825385. The contents have not been subjected to Agency review and therefore do not necessarily reflect the views of the Agency and no official endorsement should be inferred.

Technical Report Number 2000-0401
TECHNICAL REPORTS AND REPRINTS SERIES
April 2000



Department of Statistics
The Pennsylvania State University
University Park, PA 16802

G. P. Patil
Distinguished Professor and Director
Tel: (814)865-9442 Fax: (814)865-1278
Email: gpp@stat.psu.edu
<http://www.stat.psu.edu/~gpp>

Continuous Dose-Response Modeling and Risk Analysis with the Gamma and Reciprocal Gamma Distributions

Senin Banga, Ganapati P. Patil, and Charles Taillie

Center for Statistical Ecology and Environmental Statistics

Department of Statistics

The Pennsylvania State University

University Park, PA 16802

Abstract. Kodell and West (1993) describe two methods for calculating pointwise upper confidence limits on the risk function with normally distributed responses and using a certain definition of adverse quantitative effect. But Banga, Patil, and Taillie (2000b) have shown that these normal theory methods break down when applied to skew data. We accordingly develop a risk analysis model and associated likelihood-based methodology when the response follows either a gamma or reciprocal gamma distribution. The model supposes that the shape (index) parameter k of the response distribution is held fixed while the logarithm of the scale parameter is a linear model in terms of the dose level. Existence and uniqueness of the maximum likelihood estimates is established. Asymptotic likelihood-based upper and lower confidence limits on the risk are solutions of the Lagrange equations associated with a constrained optimization problem. Starting values for an iterative solution are obtained by replacing the Lagrange equations by the lowest order terms in their asymptotic expansions. Three methods are then compared for calculating confidence limits on the risk: (i) the aforementioned starting values (LRAL method), (ii) full iterative solution of the Lagrange equations (LREL method), and (iii) bounds obtained using approximate normality of the maximum likelihood estimates with standard errors derived from the information matrix (MLE method). Simulation is used to assess coverage probabilities for the resulting upper confidence limits when the log of the scale parameter is quadratic in the dose level. Results indicate that coverage for the MLE method can be off by as much as 15 percentage points and converges very slowly to nominal coverage levels as the sample size increases. Coverage for the LRAL and LREL methods, on the other hand, is close to nominal levels unless (a) the sample size is small, say $N < 25$, (b) the index parameter is small, say $k \leq 1$, and (c) the direction of adversity is to the left for the gamma distribution or to the right for the reciprocal gamma distribution.

Prepared with partial support from the Office of Research and Development, United States Environmental Protection Agency, Washington, DC under a Cooperative Agreement Number R-825385. The contents have not been subjected to Agency review and therefore do not necessarily reflect the views of the Agency and no official endorsement should be inferred.

Keywords: Benchmark dose; Confidence limits; Deviance; Likelihood contour method; Likelihood ratio; Maximum likelihood estimation.

1 Introduction

A model-based approach to the development of risk assessment methodology is an appealing alternative to the NOAEL/LOAEL approach (Chen and Gaylor, 1992; Crump, 1984; Stiteler and Durkin, 1990). For continuous responses, however, it is usually not apparent how a given response value should be dichotomized into “adverse” or “not adverse.” One solution (Chen and Gaylor, 1992; Crump, 1995; Gaylor and Slikker, 1990; Glowa, 1991; Kodell and West, 1993; West and Kodell, 1993) involves a so-called abnormal point — a response value that lies in the direction of adversity but is sufficiently far from the control mean that its occurrence in unexposed subjects would be considered unusual. Gaylor and Slikker consider the case where the abnormal point is directly specified and is a known parameter of the problem. Kodell and West take the abnormal point to be a specified number of standard deviations from the (unknown) control mean; in this approach, the abnormal point is an unknown parameter. In the present paper, the abnormal point is defined to be a specified percentile of the control distribution. For example, when the direction of adversity is toward smaller responses, the abnormal point might be taken as the 5th percentile of the control distribution. For normal distributions, the percentile definition of abnormal point is equivalent to that of Kodell and West; for more general distributions, the percentile definition has the advantage that it transforms in the same way as the response variable.

For a specified exposure level, the risk is the probability of an adverse response. Accordingly, the risk is a tail area of the response distribution for the given dose level (see Figure 1). When parametric models are specified for the response distributions, then a parametric expression can be derived for the risk as a function of the dose, which determines the ordinate of the dose response curve. Likelihood methods can then be employed to estimate the risk function and to obtain upper confidence limits on the risk. Inversion of this upper confidence curve is often used to obtain the benchmark dose level (but see Sciullo, Patil, and Taillie, 2000; Banga, Patil, and Taillie, 2000c). This program has been carried out by Kodell and West (1993) and West and Kodell (1993) when the responses are normally distributed. However, if normal theory methods are applied in a study where the data follow some other distribution, then the inferences are generally not consistent and coverage probabilities can depart markedly from nominal levels even with large sample sizes. Banga, Patil, and Taillie (2000b) have documented this effect when data arising from a gamma, reciprocal gamma, or lognormal distribution is analyzed according to normal theory methods. In fact, coverage probabilities for likelihood based confidence limits grew worse as the sample size increased from 25 to 50 to 100. The latter is apparently due to inconsistency of the likelihood estimates for a misspecified model. Applying the log transform to the data before using the normal theory methods was found to be of little help for data from the gamma and reciprocal gamma distributions.

In view of these findings, the present paper develops the continuous-response risk assessment methodology for the gamma distribution and, indirectly, for the reciprocal gamma distribution. Likelihood methods are used throughout. Members of the gamma family are

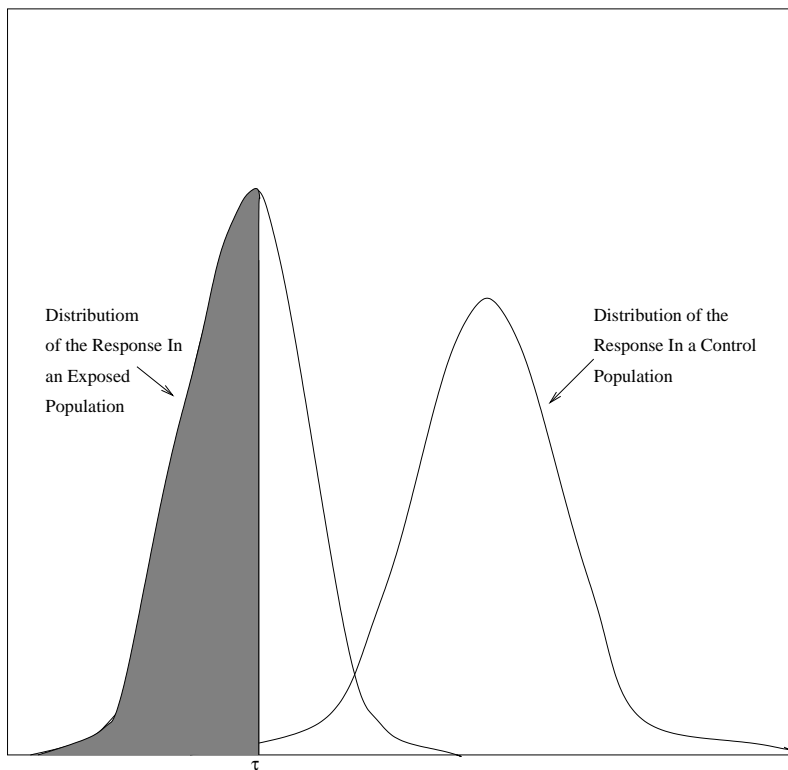


Figure 1: Schematic diagram for defining the abnormal point and corresponding risks. The abnormal point τ is a specified quantile of the control population. The shaded tail area of the response distribution for an exposed population represents the risk for that population. The risk for the control population is the background risk and will be denoted by α_τ . In the approach described here, the value of α_τ is specified by the investigator and is therefore a known specification parameter. This is different from conventional dose response analysis where the background risk is generally unknown. In our approach, it is the abnormal point τ which is unknown.

positively skewed but, compared with the lognormal, have a relatively short right-hand tail and a relatively heavy left hand-tail.

Due to symmetry, the risk assessment methodology for the normal distribution is formally the same regardless of the direction of adversity, i.e., replacing observations by their negatives reverses the direction of adversity while remaining within the normal family. Because the gamma distribution is skewed, a separate development is required depending on whether the abnormal point is in the left tail or in the right tail. Fortunately, most of the likelihood-related formulae are very similar for the two developments. From another point of view, one could replace each response y by its reciprocal $1/y$ thereby mapping the left tail into the right tail. However, the reciprocal of a gamma-distributed variate follows a reciprocal gamma distribution and not a gamma distribution. Therefore, in developing the gamma methodology for both directions of adversity we have effectively developed the methodology for the reciprocal gamma distribution as well.

Simulation studies have been conducted to assess the performance of the LR-based upper confidence limits on the risk and to compare this performance with that of confidence limits based on asymptotic normality of maximum likelihood estimators.

2 Dose Response Model for the Gamma Distribution

We suppose the dose response distributions belong to the gamma family of distributions whose shape parameter is held fixed (does not depend on dose level) and where the logarithm of the mean is a linear model in terms of the dose level. To be more specific, let

$$Y_i \sim \text{gamma}(k, \lambda_i), \quad i = 1, \dots, N$$

with

$$E(Y_i) \equiv \mu_i = k\lambda_i = e^{X_i\boldsymbol{\theta}},$$

where X_i is the i^{th} row of the design matrix X which depends on the dose level d_i and where $\boldsymbol{\theta}$ is a p -dimensional vector whose components are unknown. Also suppose that Y_1, \dots, Y_N are independent. The total sample size is

$$N = \sum_{j=1}^g n_j,$$

where g is the number of experimental dose groups and n_j is the sample size for the j^{th} dose group. The vector of unknown parameters is $\boldsymbol{\psi} = (\theta_0, \theta_1, \dots, \theta_{p-1}, k)^t$ which has dimension $q = p + 1$.

If $y(d)$ is the response at a hypothetical level d then

$$\mu(d) \equiv E(y(d)) = e^{\mathbf{x}^t\boldsymbol{\theta}}$$

where $\mathbf{x} \equiv \mathbf{x}(d)$ is a given p -dimensional vector. For example, a polynomial response model would have $\mathbf{x}_j(d) = d^{j-1}$, $j = 1, \dots, p$. The i^{th} row of the design matrix is $X_i = \mathbf{x}^t(d_i)$ where d_i is the dose level for observation i .

First, we suppose the direction of adversity is to the left. The modifications needed when the direction of adversity is to the right are given below in Section 5. Since small response values are adverse, the total risk at dose level d is

$$R(d; \boldsymbol{\psi}) = \Pr(y(d) \leq \tau | d) = F_{k, \lambda(d)}(\tau) = F_k \left(\frac{\tau}{\lambda(d)} \right) = F_k \left(\frac{\tau k}{\mu(d)} \right),$$

where $F_{k, \lambda(d)}(\cdot)$ is the distribution function of a gamma random variable with shape parameter k and scale parameter $\lambda(d)$. The function $F_k(\cdot) \equiv F_{k, 1}(\cdot)$ is the standard gamma cdf (incomplete gamma function) and τ is the abnormal point.

The background risk, α_τ , is given by

$$\alpha_\tau = \Pr(y(d) \leq \tau | d = 0) = F_k \left(\frac{\tau k}{\mu(0)} \right).$$

Throughout, we assume that τ is unknown but that α_τ is specified so that

$$\frac{\tau k}{\mu(0)} = G_k(\alpha_\tau) \quad \text{where} \quad G_k(\cdot) \equiv F_k^{-1}(\cdot).$$

We eliminate τ from the expression for $R(d)$ to obtain

$$R(d; \boldsymbol{\psi}) = F_k \left(\frac{\tau k}{\mu(d)} \right) = F_k \left(\frac{\tau k}{\mu(0)} \frac{\mu(0)}{\mu(d)} \right) = F_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \quad (1)$$

where

$$\mathbf{a} = \mathbf{x}(0) - \mathbf{x}(d).$$

This parametric expression for $R(d; \boldsymbol{\psi})$ does not involve the unknown τ ; consequently, τ does not need to be explicitly estimated for the risk calculations.

3 Maximum Likelihood Point Estimates

If Y_1, \dots, Y_N are independent and identically distributed as $\text{gamma}(k, \lambda)$, then the MLE of k and λ are unique but do not have closed-form expressions (Bowman and Shenton, 1988). Our situation is a bit more complex because the mean of the gamma distribution varies with the dose. Hence, we first establish the existence and uniqueness of the likelihood estimators for k and θ . Proofs of the results in this section are deferred to Section 8 so as to not interrupt the continuity of the presentation.

For each individual response Y_i , the negative log-likelihood function is given by

$$l_i = k(Y_i e^{-X_i \boldsymbol{\theta}} + X_i \boldsymbol{\theta}) - k \log k + \log \Gamma(k) - (k - 1) \log Y_i$$

where $\Gamma(\cdot)$ is the gamma function. It follows that

$$\begin{aligned} \frac{\partial l_i}{\partial \boldsymbol{\theta}} &= k(Y_i e^{-X_i \boldsymbol{\theta}} X_i + X_i) \\ \frac{\partial l_i}{\partial k} &= (Y_i e^{-X_i \boldsymbol{\theta}} + X_i \boldsymbol{\theta}) - \log k + \Psi(k) - \log Y_i - 1, \end{aligned}$$

where $\Psi(\cdot)$ is the digamma function (logarithmic derivative of the gamma function). The following theorem is proved in Section 8.

Theorem 1 *If the design matrix X is of full rank, then the MLE exists and is unique.*

A matrix representation of the likelihood equations is available and is given by

$$\begin{cases} X^t(\mathbf{1} - Y * e^{-X\boldsymbol{\theta}}) = \mathbf{0} \\ N(\Psi(k) - \log k) + Y^t e^{-X\boldsymbol{\theta}} - \mathbf{1}^t \log Y + \mathbf{1}^t X\boldsymbol{\theta} - N = 0 \end{cases}$$

where $\mathbf{1}$ is the N -component vector of ones, $e^{-X\boldsymbol{\theta}}$ is the componentwise exponentiation of the vector $-X\boldsymbol{\theta}$, $\log Y$ is componentwise logarithm of the vector $Y = (Y_1, \dots, Y_N)^t$, and ‘ $*$ ’ is the Hadamard (componentwise) product of two vectors.

Lemma 1 *The total negative Hessian matrix and the Fisher information matrix are given respectively by*

$$H(\boldsymbol{\theta}, k) = \begin{bmatrix} kX^tDX & X^t(\mathbf{1} - Y * e^{-X\boldsymbol{\theta}}) \\ (\mathbf{1} - Y * e^{-X\boldsymbol{\theta}})^t X & N(\Psi'(k) - \frac{1}{k}) \end{bmatrix}$$

and

$$E[H(\boldsymbol{\theta}, k)] = \begin{bmatrix} kX^tX & \mathbf{0} \\ \mathbf{0}^t & N(\Psi'(k) - \frac{1}{k}) \end{bmatrix},$$

where D is the diagonal matrix whose i^{th} diagonal entry is $Y_i e^{-X_i \boldsymbol{\theta}}$.

Due to the simple structure of the Fisher information matrix, the Newton-Raphson or Fisher scoring procedure can be used to solve numerically the likelihood equations to find the MLE of $(\boldsymbol{\theta}, k)$. Note also that the likelihood equations for $\boldsymbol{\theta}$ do not involve k , so the MLE of $\boldsymbol{\theta}$ can be found first. Then, the MLE of k is obtained by replacing $\boldsymbol{\theta}$ with $\hat{\boldsymbol{\theta}}$ in the likelihood equation for k and solving the resulting one-dimensional equation numerically. The solution of this latter equation is known to be unique.

3.1 Asymptotic variance of the estimated risk function

The following theorem provides the asymptotic variance of the estimated total risk function which is needed for calculating UCLs on the risk using asymptotic normality of the likelihood estimates (see Corollary 1 below). It is obtained from the Fisher information matrix using the method of statistical differentials. Put $\boldsymbol{\psi} = (\boldsymbol{\theta}^t, k)^t$ and let $f_k(x)$ be the density function of the standard gamma with shape parameter k . We consider a fixed value d for the dose and write

$$\boldsymbol{\omega}^2 = \mathbf{a}^t (X^t X)^{-1} \mathbf{a},$$

where $\mathbf{a} = \mathbf{x}(0) - \mathbf{x}(d)$ is known. We also put

$$W(x, k) = x^k \sum_{n=0}^{\infty} \frac{(-1)^n x^n}{n!(n+k)^2}.$$

Lemma 2

$$\frac{\partial}{\partial \boldsymbol{\theta}} R(d; \boldsymbol{\psi}) = k f_{k+1} \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \mathbf{a} \quad (2)$$

and

$$\frac{\partial}{\partial k} R(d; \boldsymbol{\psi}) = A_{\alpha_\tau}(\boldsymbol{\theta}, k) + B_{\alpha_\tau}(\boldsymbol{\theta}, k), \quad (3)$$

where

$$\begin{aligned} A_{\alpha_\tau}(\boldsymbol{\theta}, k) &= \left\{ \left(\Psi(k) - \log G_k(\alpha_\tau) \right) \alpha_\tau + W \left(G_k(\alpha_\tau), k \right) / \Gamma(k) \right\} \times \\ &\quad \exp \left\{ \left(\mathbf{a}^t \boldsymbol{\theta} \right) k - \left(e^{\mathbf{a}^t \boldsymbol{\theta}} - 1 \right) G_k(\alpha_\tau) \right\}, \\ B_{\alpha_\tau}(\boldsymbol{\theta}, k) &= \left(\mathbf{a}^t \boldsymbol{\theta} + \log G_k(\alpha_\tau) - \Psi(k) \right) F_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) - W \left(G_k(\alpha_\tau) \mathbf{a}^t \boldsymbol{\theta}, k \right) / \Gamma(k) \\ &= \left(\mathbf{a}^t \boldsymbol{\theta} + \log G_k(\alpha_\tau) - \Psi(k) \right) R(d; \boldsymbol{\psi}) - W \left(G_k(\alpha_\tau) \mathbf{a}^t \boldsymbol{\theta}, k \right) / \Gamma(k). \end{aligned}$$

Theorem 2 For each fixed dose level d , the parameter $R(d; \boldsymbol{\psi}) - R(d; \hat{\boldsymbol{\psi}})$ is asymptotically distributed as $N(0, \sigma_d^2)$, where

$$\sigma_d^2 = \left(A_{\alpha_\tau}(\boldsymbol{\theta}, k) + B_{\alpha_\tau}(\boldsymbol{\theta}, k) \right)^2 \frac{k}{N(k\Psi'(k) - 1)} + k \omega^2 f_{k+1}^2 \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right).$$

A consistent estimator of σ_d^2 is obtained by replacing $\boldsymbol{\theta}$ and k with $\hat{\boldsymbol{\theta}}$ and \hat{k} , respectively.

Corollary 1 For a given dose level d , an asymptotic $100(1 - \alpha)\%$ one-sided UCL for the total risk, $R(d; \boldsymbol{\psi})$, is given by

$$R(d; \hat{\boldsymbol{\psi}}) + z_{1-\alpha} \hat{\sigma}_d,$$

where $z_{1-\alpha}$ is the $100(1 - \alpha)$ th percentile of the standard normal distribution.

Our simulations have shown that the UCL given by Corollary 1 has very poor coverage even for large sample sizes. We accordingly turn to UCLs based on the likelihood ratio statistic (Crump and Howe, 1983; Rao, 1947).

4 LRT-Based Confidence Limits for the Risk Function

This approach relies on the duality between hypothesis testing and confidence intervals. Instead of finding an asymptotic pivotal quantity for the total risk as in Corollary 1, we cast the problem of finding the UCLs in terms of hypothesis testing:

$$H_o : R(d; \boldsymbol{\psi}) = c \quad \text{versus} \quad H_A : R(d; \boldsymbol{\psi}) < c$$

for some constant c . Using the likelihood ratio test, the test statistic is

$$\mathcal{D}(\tilde{\boldsymbol{\psi}}) = 2(l(\tilde{\boldsymbol{\psi}}) - l(\hat{\boldsymbol{\psi}})),$$

where $\tilde{\boldsymbol{\psi}}$ is the MLE of $\boldsymbol{\psi}$ under H_o . The statistic $\mathcal{D}(\tilde{\boldsymbol{\psi}})$ is asymptotically distributed as χ_1^2 under H_o .

4.1 Likelihood contour method

In the above, if we reject H_0 for some value of c , then we should reject H_0 for all larger values of c . A $100(1 - \alpha)\%$ UCL on $R(d; \boldsymbol{\psi})$ is the value c that is transitional between acceptance and rejection of the null hypothesis, that is, the maximum value of $R(d; \boldsymbol{\psi})$ for which $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$, where $\chi_{1, 1-2\alpha}^2$ is the $100(1 - 2\alpha)\%$ th percentile of the χ_1^2 distribution. Hence, to find an asymptotic $100(1 - \alpha)\%$ UCL on the risk, we maximize $R(d; \boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$. This is summarized in the following theorem (see Figure 2):

Theorem 3 (Likelihood ratio confidence intervals)

1. An asymptotic $100(1 - \alpha)\%$ two-sided confidence interval for the scalar parameter $\varphi = R(d; \boldsymbol{\psi})$ is given by

$$\varphi_l \leq \varphi \leq \varphi_u,$$

where φ_u is the maximum of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$ and φ_l is the minimum of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$.

2. An asymptotic $100(1 - \alpha)\%$ one-sided UCL for $\varphi = R(d; \boldsymbol{\psi})$ is the maximum φ_u of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$. Similarly, an asymptotic $100(1 - \alpha)\%$ one-sided LCL for $\varphi = R(d; \boldsymbol{\psi})$ is the minimum φ_l of $\varphi(\boldsymbol{\psi})$ subject to $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$.

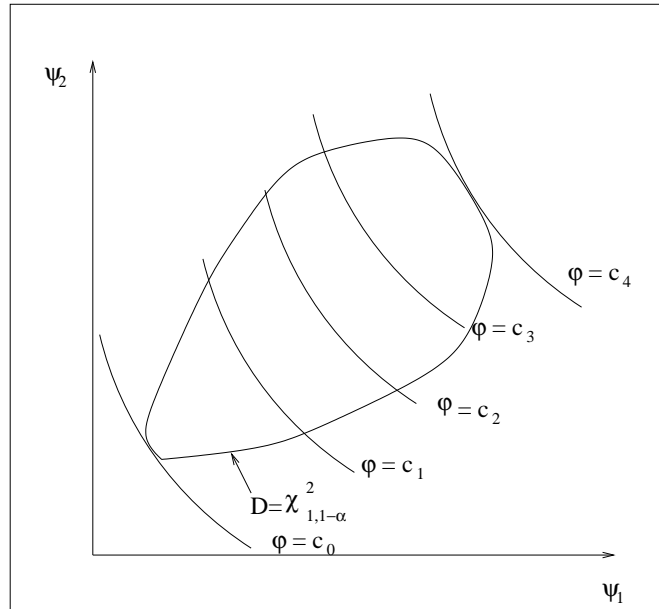


Figure 2: Two-dimensional schematic for LR-based confidence limits for the scalar parameter $\varphi = R(d; \boldsymbol{\psi})$. The constants $c_0 < c_1 < c_2 < c_3 < c_4$ label various contours of φ . A one-sided UCL for φ is $\varphi = c_4$ which is obtained by maximizing φ along the contour $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2$. Similarly, c_0 is an LCL for φ .

For our purposes, item 2 is the one of interest as we will be concerned with upper confidence limits on the risk. The Lagrange equations for this constrained optimization

problem are given by (we use ξ for the Lagrange multiplier since λ is the scale parameter of the gamma distribution):

$$\begin{cases} \nabla \mathcal{D}(\boldsymbol{\psi}) - \xi \nabla R(d; \boldsymbol{\psi}) = \mathbf{0} \\ \mathcal{D}(\boldsymbol{\psi}) = \chi_{1, 1-2\alpha}^2 \end{cases} \quad (4)$$

where

$$\nabla R(d, \boldsymbol{\psi}) = \begin{bmatrix} k f_{k+1} \left(G_k(\alpha_\tau) e^{\mathbf{a}' \boldsymbol{\theta}} \right) \mathbf{a} \\ A_{\alpha_\tau}(\boldsymbol{\theta}, k) + B_{\alpha_\tau}(\boldsymbol{\theta}, k) \end{bmatrix}. \quad (5)$$

In case of the homoscedastic normal model, Banga, Patil and Taillie (2000a) found an analytic solution (up to a simple one-dimensional optimization problem) for the corresponding Lagrange equations. For the gamma model described here, no analytical simplification is evident and the equations need to be solved numerically. Numerical study of the equations suggests that there are exactly two solutions in $(\boldsymbol{\theta}, k, \xi)$, leading respectively to an upper and a lower confidence limit. The theoretical possibility of multiple solutions remains open, however.

Iterative solution of Lagrange equations is usually very sensitive to the choice of starting values. The next section describes how good starting values can be obtained.

4.2 Asymptotic approximations to the Lagrange equations: Starting values

Regardless of the response distribution, Banga, Patil and Taillie (2000a) have shown that when the Lagrange equations are replaced by the lowest order terms in their asymptotic expansions, the resulting equations have exactly two solutions corresponding to the upper and lower confidence limits, respectively. Further, they have given explicit expressions for these two solutions in terms of the maximum likelihood point estimates. For the gamma model, the solution of the approximate Lagrange equations corresponding to the UCL on the risk is given by

$$\boldsymbol{\psi}_a = \hat{\boldsymbol{\psi}} + \frac{\sqrt{\chi_{1, 1-2\alpha}^2} H^{-1}(\hat{\boldsymbol{\psi}}) \nabla R(d; \hat{\boldsymbol{\psi}})}{\sqrt{[\nabla R(d; \hat{\boldsymbol{\psi}})]^t H^{-1}(\hat{\boldsymbol{\psi}}) \nabla R(d; \hat{\boldsymbol{\psi}})}} \quad (6)$$

where the negative Hessian matrix $H(\boldsymbol{\psi})$ is given in Lemma 1 and an expression for $\nabla R(d; \boldsymbol{\psi})$ appears in equation (5). The negative Hessian matrix in this formula can be replaced by the information matrix (Lemma 1), which is asymptotically equivalent but analytically simpler for the gamma model.

The approximate solution $\boldsymbol{\psi}_a$ is used as starting value for iterative solution of the Lagrange equations; $\boldsymbol{\psi}_a$ is usually so close to the exact solution that only a few iterations are needed to achieve convergence.

We have described two different ways of calculating a UCL on the risk from the asymptotic distribution of the likelihood ratio statistic. The first method consists of solving the Lagrange equations iteratively to obtain the “exact” solution $\boldsymbol{\psi}^*$. We then compute the asymptotic UCL at dose level d as $R(d; \boldsymbol{\psi}^*)$. We call this method as **LREL** where the “EL” stands for exact solution of the Lagrange equations. The second method calculates the UCL as $R(d; \boldsymbol{\psi}_a)$ where $\boldsymbol{\psi}_a$ is the solution given above for the approximate Lagrange equations. We

call this approach as **LRAL** where “AL” stands for the approximate Lagrange equations. Section 6 compares the coverage probabilities of the LREL and LRAL methods, as well as the MLE method of Corollary 1, for the gamma model.

5 Large Responses Are Adverse

This section develops the risk analysis for the gamma distribution where large instead of small responses are classified as adverse. Continuing with the same notations, the total and background risks are respectively given by

$$R(d; \boldsymbol{\psi}) = \Pr(Y_i \geq \tau|d) \quad \text{and} \quad \alpha_\tau = \Pr(Y_i \geq \tau|d = 0).$$

The parametric expression for the total risk becomes

$$R(d; \boldsymbol{\psi}) = 1 - F_k \left(G_k(1 - \alpha_\tau)e^{\mathbf{a}^t \boldsymbol{\theta}} \right)$$

after eliminating τ as before. This may be compared with equation (1).

The likelihood equations and the Hessian and Fisher information matrices remain unchanged since the model is the same. Even though the risk functions in both scenarios are conceptually different, their analytical expressions are so closely related that one can obtain the asymptotic variance (MLE approach) and the Lagrange equations (LR approach) from the previous results with only minor adjustments. Specifically, let $\boldsymbol{\psi}$, $f_k(x)$, ω , \mathbf{a} , $W(x, k)$, A_{α_τ} , and B_{α_τ} be as defined previously. Consider a fixed d value for the dose. Lemma 2 provides the derivatives of functions of the form $F_k(k(\alpha_\tau)e^{\mathbf{a}^t \boldsymbol{\theta}})$ with respect to $\boldsymbol{\theta}$ and k . Adjusting for the sign and replacing α_τ with $1 - \alpha_\tau$ the corresponding derivatives for the new risk are given by

$$\frac{\partial}{\partial \boldsymbol{\theta}} R(d; \boldsymbol{\psi}) = -k f_{k+1} \left(G_k(1 - \alpha_\tau)e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \mathbf{a}$$

and

$$\frac{\partial}{\partial k} R(d; \boldsymbol{\psi}) = -A_{1-\alpha_\tau}(\boldsymbol{\theta}, k) - B_{1-\alpha_\tau}(\boldsymbol{\theta}, k).$$

It follows that the variance of the estimated risk $R(d; \hat{\boldsymbol{\psi}})$ is

$$\sigma_d^2 = \left(A_{1-\alpha_\tau}(\boldsymbol{\theta}, k) + B_{1-\alpha_\tau}(\boldsymbol{\theta}, k) \right)^2 \frac{k}{N(k\Psi'(k) - 1)} + k \omega^2 f_{k+1}^2 \left(G_k(1 - \alpha_\tau)e^{\mathbf{a}^t \boldsymbol{\theta}} \right).$$

For a given dose level d , an asymptotic $100(1 - \alpha)\%$ one-sided UCL on the total risk, $R(d; \boldsymbol{\psi})$, based on the MLE method is

$$R(d; \hat{\boldsymbol{\psi}}) + z_{1-\alpha} \hat{\sigma}_d,$$

where $\hat{\sigma}_d$, a consistent estimator of σ_d , is obtained by replacing $\boldsymbol{\theta}$ and k by $\hat{\boldsymbol{\theta}}$ and \hat{k} . The new Lagrange equations and starting values are obtained by using

$$\nabla R(d; \boldsymbol{\psi}) = - \left[\begin{array}{c} k f_{k+1} \left(G_k(1 - \alpha_\tau)e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \mathbf{a} \\ A_{1-\alpha_\tau}(\boldsymbol{\theta}, k) + B_{1-\alpha_\tau}(\boldsymbol{\theta}, k) \end{array} \right] \quad (7)$$

in equations (4) and (6), respectively.

6 Simulation Studies

Two simulation studies are conducted to assess the performance of the LR and the MLE methods in terms of the coverage probabilities of the upper confidence limits on the risk. In the first study, the direction of adversity is to the left and in the second study the direction of adversity is to the right. *Mathematica* is the primary software used to conduct these studies. In particular, the equation solver in *Mathematica* was used for iterative solution of the Lagrange equations with the starting values described above.

6.1 Study I (Small responses are adverse)

We conduct this simulation study to evaluate and compare the performance of the three methods (LREL, LRAL and MLE) in the case where small responses are classified as adverse. Asymptotic 95% UCLs on the risk are calculated based on the three methods. There is a total of six experiments in this study, each of which is determined by the shape parameter k in the model

$$y(d) \sim \text{Gamma}(k, \lambda(d)) \quad \text{with} \quad E(y(d)) = k\lambda(d) = e^{3-d-.1d^2},$$

where the parameter k takes the values 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0.

For each of these six models there are five dose groups: a control group ($d = 0$) and four treatment or experimental dose groups d_1 , d_2 , d_3 , and d_4 . The experimental dose levels are varied so that they yield the same true risk across the six experiments. With this setup, experiment-to-experiment differences can be attributed to distributional changes as the parameter k changes in the study. The background risk in each of the six experiments is specified as $\alpha_\tau = 0.05$. In addition, each dose group is simulated with first 5 ($n_i = 5$, $N = 25$), then 10 ($n_i = 10$, $N = 50$) and finally 20 ($n_i = 20$, $N = 100$) observations. Asymptotic 95% UCLs in each of the 3 designs of the 6 experiments are calculated for 4000 replicates. The estimated coverage probability in each case is computed as the proportion of the 4000 simulations for which the resulting UCLs are greater than or equal to the true risk. Since the targeted coverage probability is 95 percent, the simulation error for the computed coverage has an approximate standard deviation of $\sqrt{.95(.05)/4000} = .003$ or 0.3 percentage points. Figures 3, 4 and 5 summarize our findings.

6.2 Study II (Large responses are adverse)

A similar simulation study is conducted for the case where the direction of adversity is to the right. Each of the six experiments in this study is determined by the parameter k in the model

$$y(d) \sim \text{Gamma}(k, \lambda(d)) \quad \text{with} \quad E(y(d)) = k\lambda(d) = e^{3+d+.1d^2},$$

where, as above, k takes the values 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0. Figures 6, 7 and 8 summarize our findings.

7 Discussion

We have shown how the continuous-response risk analysis methodology can be developed for non-normal distributional models, specifically the gamma distribution. The simulation results show that the LR-based procedures provide far better coverage probabilities than the MLE method. As the sample size increases the LRAL procedure improves rapidly and provides coverage probabilities that are very close to the nominal coverage probabilities as well as to those obtained from the LREL approach. The MLE method on the other hand is slow to improve as the sample size increases. Even for sample sizes as large as 100, it yields coverage probabilities that are still far from the nominal levels.

The direction of adversity does not seem to play a major role in the performance of the procedures. All three methods do give coverage that is somewhat closer to nominal when the direction of adversity is to the right. When the direction of adversity is to the left, the LRAL method gives under-coverage compared with the LREL. When the direction of adversity is to the right, the LRAL and LREL are so close that no reliable comparison can be made.

Moreover, comparisons of the coverage probabilities for different values of the shape parameter k do not reveal any systematic pattern as to the improvement or non-improvement of the three procedures except that LRAL and LREL have tendency toward under-coverage when $k \leq 1$, N is small, and the direction of adversity is to the left.

8 Proof of Results for Section 3

In this Section, we provide proofs and derivations for the main results in Section 3. For each individual response Y_i in the gamma model, the negative log-likelihood function is given by

$$l_i = k(Y_i e^{-X_i \boldsymbol{\theta}} + X_i \boldsymbol{\theta}) - k \log k + \log \Gamma(k) - (k - 1) \log Y_i.$$

The total negative log-likelihood function for the model can be written as

$$l = \sum l_i = k Y^t e^{-X \boldsymbol{\theta}} + k \mathbf{1}^t X \boldsymbol{\theta} - N k \log k + N \log \Gamma(k) - (k - 1) \mathbf{1}^t \log Y.$$

It follows that

$$\frac{\partial l}{\partial \boldsymbol{\theta}} = k X^t (\mathbf{1} - Y * e^{-X \boldsymbol{\theta}})$$

and

$$\frac{\partial l}{\partial k} = N(\Psi(k) - \log k) + Y^t e^{-X \boldsymbol{\theta}} - \mathbf{1}^t \log Y + \mathbf{1}^t X \boldsymbol{\theta} - N$$

where $\Psi(\cdot)$ is the digamma function.

8.1 Proof of Theorem 1

We note that the likelihood equations for $\boldsymbol{\theta}$ do not involve k and, for given $\boldsymbol{\theta}$, the likelihood equation for k has a unique solution because the function $\Psi(k) - \log k$ is strictly increasing. Thus, we can treat k as fixed and show that the MLE of $\boldsymbol{\theta}$ exists and is unique. We first prove the uniqueness and then the existence.

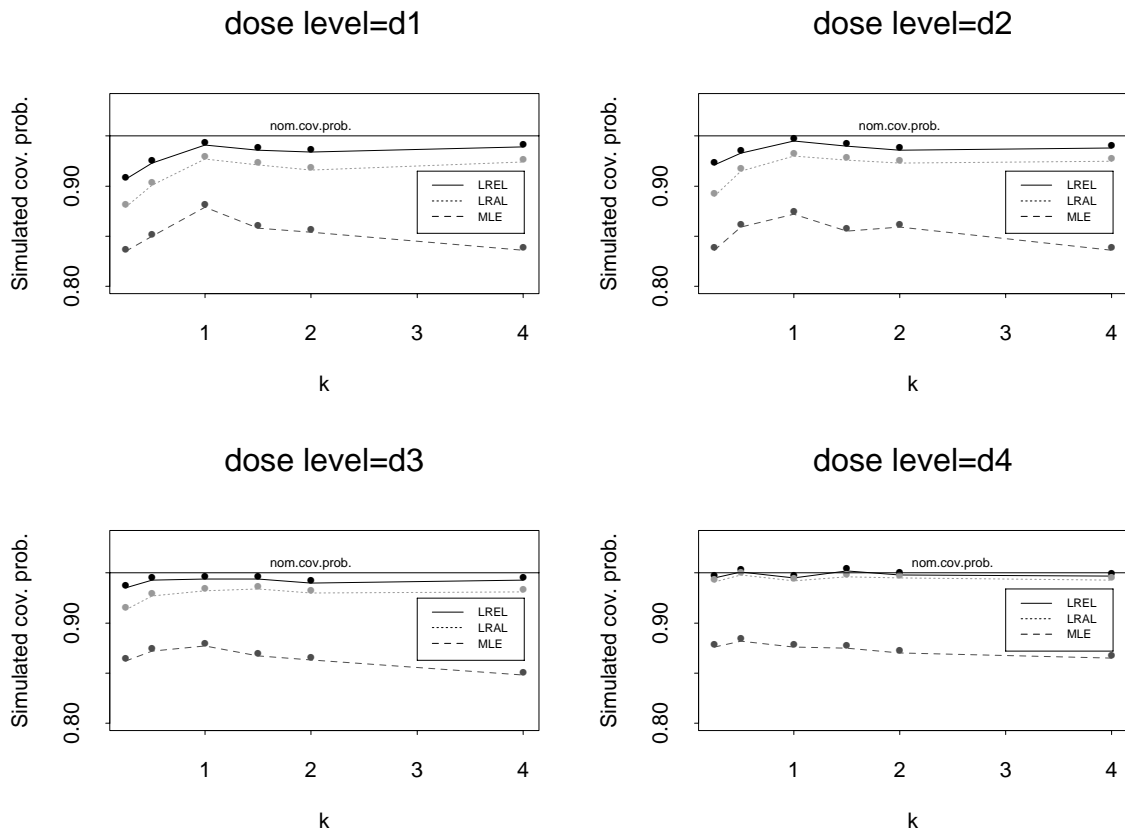


Figure 3: Simulated coverage probabilities for gamma model with direction of adversity to the **left**. The targeted coverage probability is 0.95. Each experimental dose group consists of **5** animals so that the total sample size is $N = \mathbf{25}$. The standard error of simulation is about 0.3 percentage points.

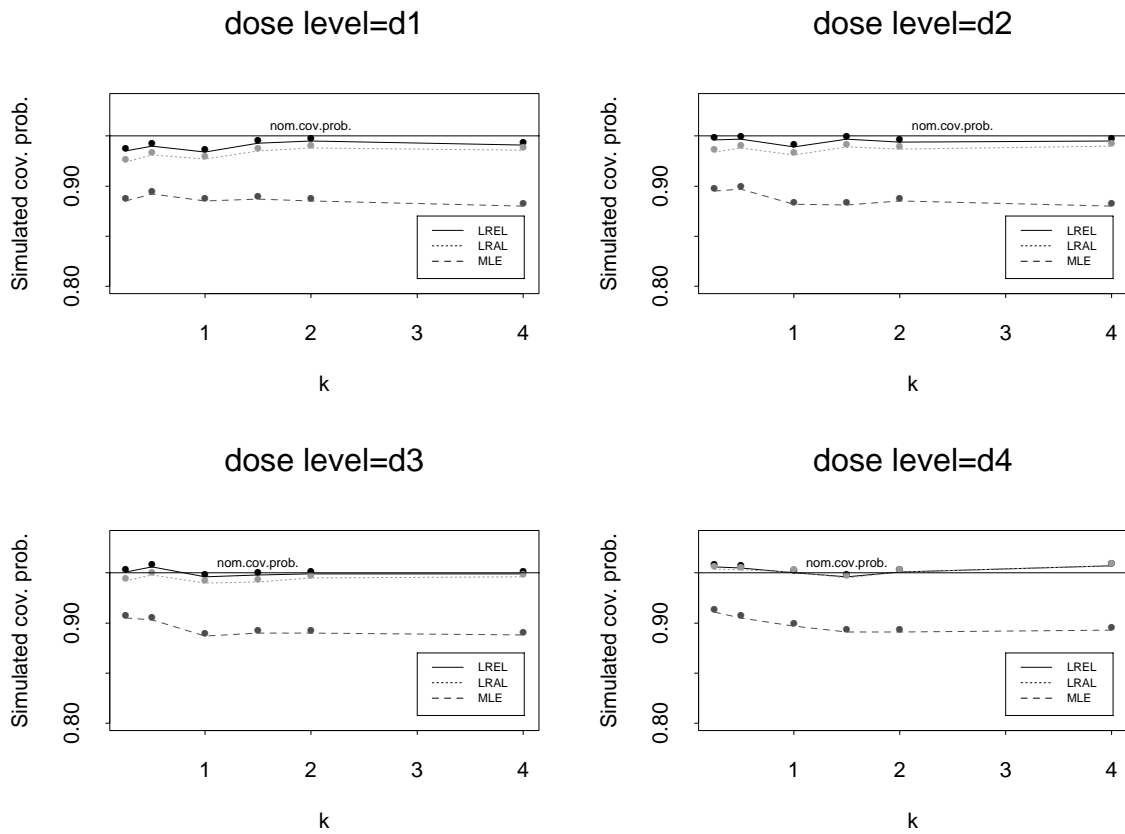


Figure 4: Simulated coverage probabilities for gamma model with direction of adversity to the **left**. The targeted coverage probability is 0.95. Each experimental dose group consists of **10** animals so that the total sample size is $N = 50$. The standard error of simulation is about 0.3 percentage points.

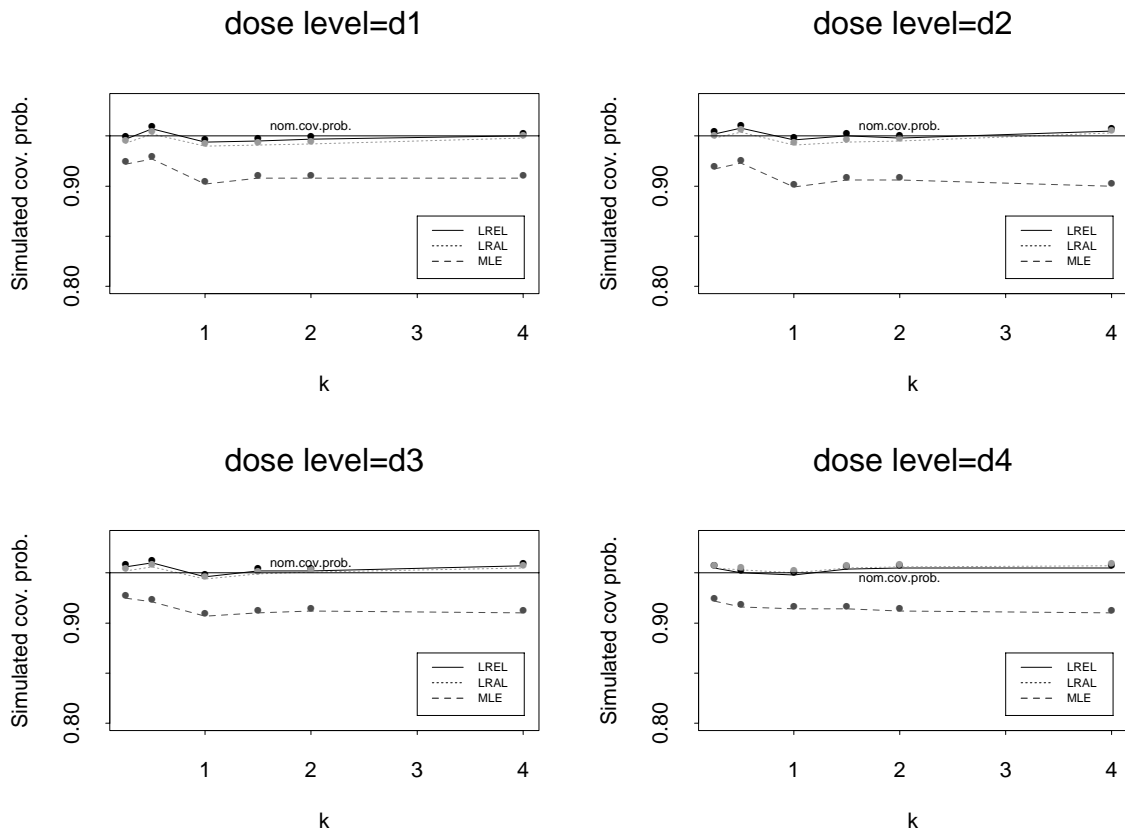


Figure 5: Simulated coverage probabilities for gamma model with direction of adversity to the **left**. The targeted coverage probability is 0.95. Each experimental dose group consists of **20** animals so that the total sample size is $N = \mathbf{100}$. The standard error of simulation is about 0.3 percentage points.

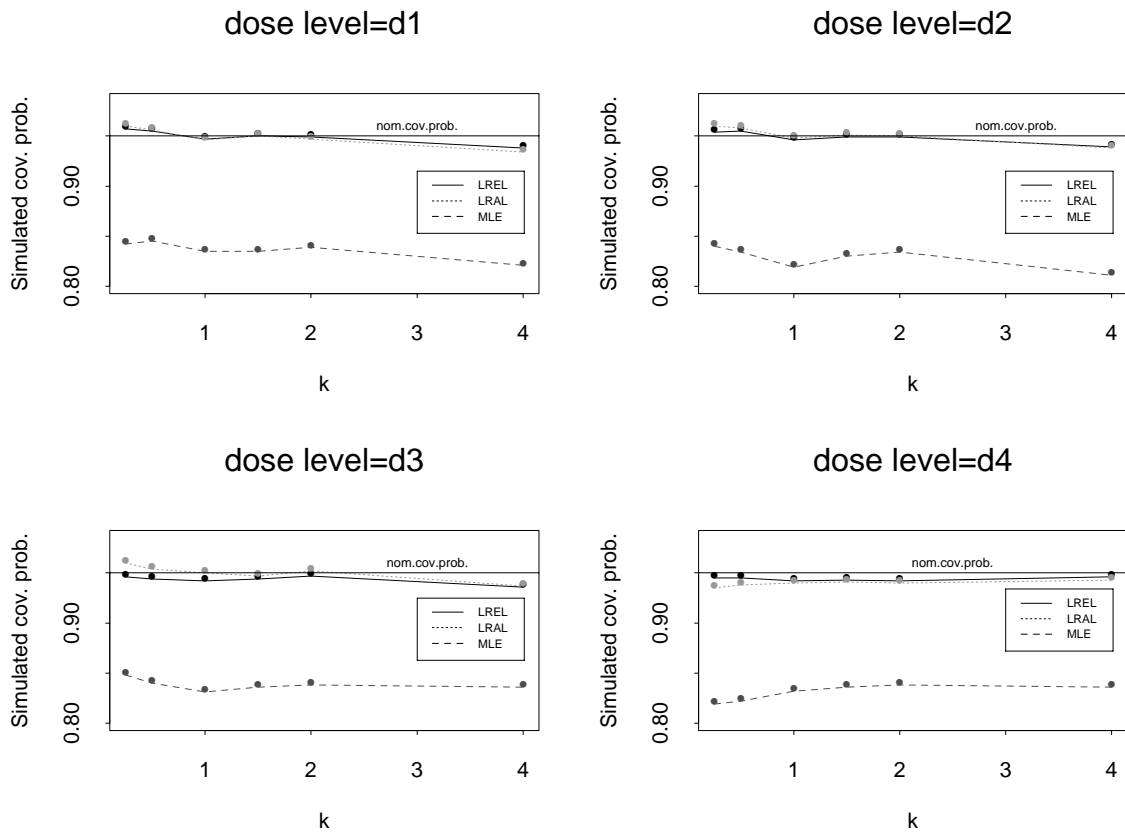


Figure 6: Simulated coverage probabilities for gamma model with direction of adversity to the **right**. The targeted coverage probability is 0.95. Each experimental dose group consists of **5** animals so that the total sample size is $N = \mathbf{25}$. The standard error of simulation is about 0.3 percentage points.

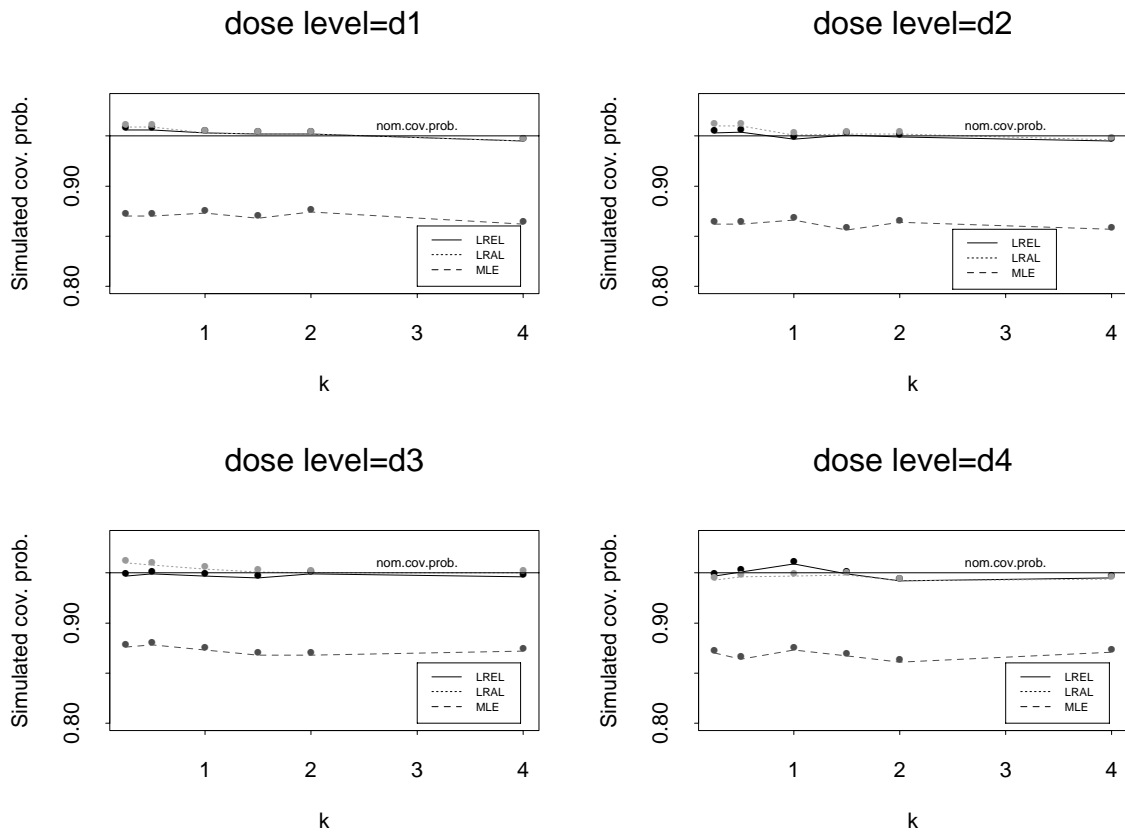


Figure 7: Simulated coverage probabilities for gamma model with direction of adversity to the **right**. The targeted coverage probability is 0.95. Each experimental dose group consists of **10** animals so that the total sample size is $N = 50$. The standard error of simulation is about 0.3 percentage points.

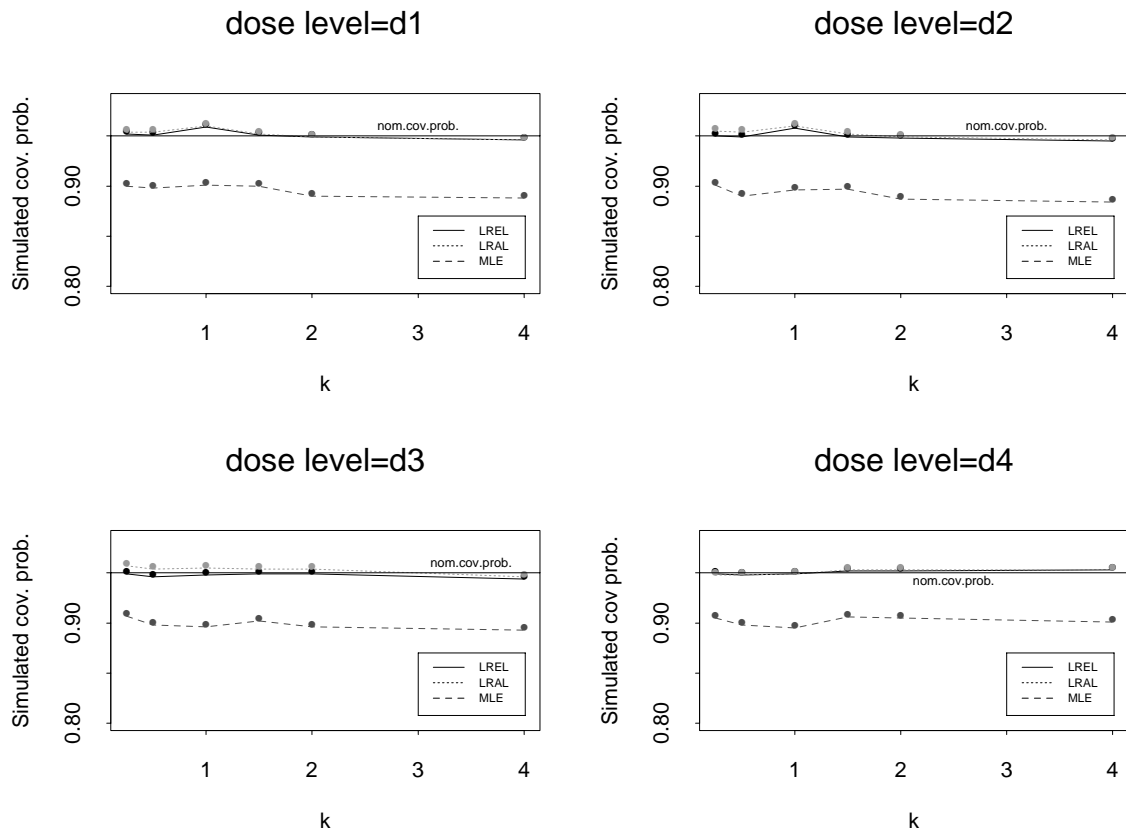


Figure 8: Simulated coverage probabilities for gamma model with direction of adversity to the **right**. The targeted coverage probability is 0.95. Each experimental dose group consists of **20** animals so that the total sample size is $N = \mathbf{100}$. The standard error of simulation is about 0.3 percentage points.

Uniqueness. It is enough to show that the negative logarithm of the likelihood, l , is strictly convex as a function of $\boldsymbol{\theta}$ with k fixed. But, for any $1 \leq r, s \leq p$,

$$\frac{\partial^2 l_i}{\partial \theta_r \partial \theta_s} = k(e^{-X_i \boldsymbol{\theta}} Y_i X_{ir} X_{is})$$

so that $\frac{\partial^2 l}{\partial \theta_r \partial \theta_s}$ has the form $X^t D X$ where D is a diagonal matrix with

$$D_{ii} = e^{-X_i \boldsymbol{\theta}} Y_i > 0.$$

Since D is positive definite and X is of full rank, $X^t D X$ is positive definite. Hence, if the MLE of $\boldsymbol{\theta}$ exists it is unique.

Existence. To establish existence, we show that $l \rightarrow \infty$ as $|\boldsymbol{\theta}| \rightarrow \infty$. Write $\mu_i = e^{X_i \boldsymbol{\theta}}$. The essential part of l_i is

$$\frac{Y_i}{\mu_i} + \log \mu_i.$$

This expression is bounded below and it approaches infinity as either $\mu_i \rightarrow 0$ or $\mu_i \rightarrow +\infty$. It follows that l is bounded below and $l \rightarrow +\infty$ when there is even one i for which $\mu_i \rightarrow 0$ or $\mu_i \rightarrow +\infty$. We now let $|\boldsymbol{\theta}| \rightarrow \infty$ along lines passing through the origin, that is,

$$\boldsymbol{\theta} = t \boldsymbol{\theta}_o \quad \text{where} \quad -\infty < t < \infty \quad \text{and} \quad \boldsymbol{\theta}_o \neq \mathbf{0}.$$

Since X is of full rank and $\boldsymbol{\theta}_o \neq \mathbf{0}$, there is at least one i for which $X_i \boldsymbol{\theta}_o \neq 0$. Then $X_i \boldsymbol{\theta} = t X_i \boldsymbol{\theta}_o \rightarrow \pm\infty$ as $t \rightarrow \pm\infty$. This implies that $\mu_i = e^{X_i \boldsymbol{\theta}} \rightarrow 0, \infty$ as $t \rightarrow \pm\infty$ and the proof is completed.

8.2 Proof of Lemma 1

We have

$$\frac{\partial^2 l}{\partial \boldsymbol{\theta}^2} = k X^t D X \quad \text{and} \quad E \left[\frac{\partial^2 l}{\partial \boldsymbol{\theta}^2} \right] = k X^t X,$$

where D is a diagonal matrix with

$$D_{ii} = e^{-X_i \boldsymbol{\theta}} Y_i.$$

Moreover,

$$\frac{\partial^2 l}{\partial \boldsymbol{\theta} \partial k} = X^t (\mathbf{1} - Y * e^{-X \boldsymbol{\theta}}) \quad \text{so that} \quad E \left[\frac{\partial^2 l}{\partial \boldsymbol{\theta} \partial k} \right] = \mathbf{0} \quad \text{since} \quad E[Y] = e^{-X \boldsymbol{\theta}}.$$

Also,

$$\frac{\partial^2 l}{\partial k^2} = N \left(\Psi'(k) - \frac{1}{k} \right) \quad \text{and} \quad E \left[\frac{\partial^2 l}{\partial k^2} \right] = N \left(\Psi'(k) - \frac{1}{k} \right).$$

Hence, the total negative Hessian and Fisher information matrices are as given in Lemma 1.

8.3 Proof of Lemma 2

Recall that

$$R(d; \psi) = F_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \quad \text{and} \quad W(x, k) = x^k \sum_{n=0}^{\infty} \frac{(-1)^n x^n}{n!(n+k)^2},$$

where $F_k(\cdot)$ and $G_k(\cdot)$ are respectively the CDF and the inverse CDF of the standard gamma distribution. Before proving Lemma 2, we state and prove the following result.

Lemma 3

$$\frac{\partial}{\partial k} F_k(x) = F_k(x)(\log x - \Psi(k)) - \frac{W(x, k)}{\Gamma(k)}, \quad x > 0 \quad (8)$$

$$\frac{d}{dk} G_k(y) = \frac{(\Psi(k) - \log G_k(y)) y + W(G_k(y), k)/\Gamma(k)}{f_k(G_k(y))}, \quad 0 < y < 1 \quad (9)$$

$$\int_0^x f_k(y) \log y \, dy = F_k(x) \log x - W(x, k)/\Gamma(k), \quad x > 0. \quad (10)$$

Proof. To prove (8), we write

$$F_k(x) = 1 - \frac{\Gamma(k, x)}{\Gamma(k)} \quad \text{where} \quad \Gamma(k, x) = \int_x^{\infty} t^{k-1} e^{-t} dt,$$

so that

$$\frac{\partial}{\partial k} F_k(x) = \Psi(k)(1 - F_k(x)) - \left[\frac{\partial}{\partial k} \Gamma(k, x) \right] / \Gamma(k).$$

But, $\Gamma(k, x)$ can be written as (see Andrews, 1985):

$$\Gamma(k, x) = \Gamma(k) - x^k \sum_{n=0}^{\infty} \frac{(-1)^n x^n}{n!(n+k)}, \quad (11)$$

so that

$$\frac{\partial \Gamma(k, x)}{\partial k} = \Gamma'(k) - (\Gamma(k) - \Gamma(k, x)) \log x + W(x, k)$$

and it follows that

$$\frac{\partial F_k(x)}{\partial k} = F_k(x)(\log x - \Psi(k)) - \frac{W(x, k)}{\Gamma(k)}.$$

To establish (9), we let $x = G_k(y)$ so that $F_k(x) = y$. Also, let y be fixed so that $x = x(k)$. Then,

$$\frac{d F_k(x)}{dk} = \frac{\partial F_k(x)}{\partial x} \frac{dx}{dk} + \frac{\partial F_k(x)}{\partial k} = 0.$$

Thus,

$$\frac{dx}{dk} = -\frac{\frac{\partial F_k(x)}{\partial k}}{f_k(x)}.$$

Equation (9) results from substituting the above expression for $\frac{\partial}{\partial k}F_k(x)$ and replacing x by $G_k(y)$. Finally, (10) is obtained by writing

$$\int_0^x f_k(y) \log y \, dy = \frac{\partial \gamma(k, x)}{\partial k} / \Gamma(k),$$

where

$$\gamma(k, x) = \int_0^x y^{k-1} e^{-y} dy = \Gamma(k) - \Gamma(k, x).$$

Thus,

$$\int_0^x f_k(y) \log y \, dy = \frac{\Gamma'(k) - \frac{\partial \Gamma(k, x)}{\partial k}}{\Gamma(k)}.$$

We then substitute the expression for $\frac{\partial \Gamma(k, x)}{\partial k}$, as given in equation (11), to obtain

$$\int_0^x f_k(y) \log y \, dy = F_k(x) \log x - \frac{W(x, k)}{\Gamma(k)}$$

This completes the proof of Lemma 3.

We are now ready to prove Lemma 2. Recall that

$$R(d; \boldsymbol{\psi}) = F_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right).$$

We have

$$\frac{\partial R(d; \boldsymbol{\psi})}{\partial \boldsymbol{\theta}} = G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} f_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \mathbf{a}$$

and this simplifies into the expression given in (2) since $x f_k(x) = k f_{k+1}(x)$. On the other hand, by the Leibnitz rule,

$$\frac{\partial R(d; \boldsymbol{\psi})}{\partial k} = e^{\mathbf{a}^t \boldsymbol{\theta}} f_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right) \frac{d}{dk} G_k(\alpha_\tau) + \int_0^{G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}}} \frac{\partial f_k(y)}{\partial k} dy.$$

The first term in the above leads to $A_{\alpha_\tau}(\boldsymbol{\theta}, k)$ by direct substitution of the expression $\frac{d}{dk} G_k(\alpha_\tau)$ as given in (9). The second term corresponds to $B_{\alpha_\tau}(\boldsymbol{\theta}, k)$ and can be written as

$$\int_0^{G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}}} \log y f_k(y) dy - \Psi(k) F_k \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right)$$

since

$$\frac{\partial f_k(y)}{\partial k} = (\log y - \Psi(k)) f_k(y).$$

The expression for $B_{\alpha_\tau}(\boldsymbol{\theta}, k)$ as given in Lemma 2 is obtained by direct application of equation (10).

8.4 Proof of Theorem 2

At any given dose level d , the Taylor expansion of the total risk about $\hat{\boldsymbol{\psi}}$, the MLE of $\boldsymbol{\psi}$, is given by

$$R(d; \boldsymbol{\psi}) = R(d; \hat{\boldsymbol{\psi}}) + (k - \hat{k}) \frac{\partial}{\partial k} R(d; \hat{\boldsymbol{\psi}}) + (\boldsymbol{\theta} - \hat{\boldsymbol{\theta}})^t \frac{\partial}{\partial \boldsymbol{\theta}} R(d; \hat{\boldsymbol{\psi}}) + O_p\left(\frac{1}{\sqrt{N}}\right)$$

and therefore,

$$R(d; \hat{\boldsymbol{\psi}}) - R(d; \boldsymbol{\psi}) = (\hat{k} - k) \frac{\partial}{\partial k} R(d; \hat{\boldsymbol{\psi}}) + (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})^t \frac{\partial}{\partial \boldsymbol{\theta}} R(d; \hat{\boldsymbol{\psi}}) + O_p\left(\frac{1}{\sqrt{N}}\right).$$

But, $\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}$ is asymptotically multivariate normal with mean vector $\mathbf{0}$ and covariance matrix $(E[H(\boldsymbol{\psi})])^{-1}$ given by

$$\begin{bmatrix} \frac{(X^t X)^{-1}}{k} & \mathbf{0} \\ \mathbf{0}^t & \frac{k}{N(k\Psi'(k)-1)} \end{bmatrix}.$$

By the Cramer-Wold Theorem $R(d; \hat{\boldsymbol{\psi}}) - R(d; \boldsymbol{\psi})$ is asymptotically univariate normal with mean 0 and variance

$$\sigma_d^2 = \left[\frac{\partial R(d; \boldsymbol{\psi})}{\partial \boldsymbol{\theta}}, \frac{\partial R(d; \boldsymbol{\psi})}{\partial k} \right] (E[H(\boldsymbol{\psi})])^{-1} \left[\frac{\partial R(d; \boldsymbol{\psi})}{\partial \boldsymbol{\theta}}, \frac{\partial R(d; \boldsymbol{\psi})}{\partial k} \right]^t.$$

By Lemma 2, this becomes

$$\sigma_d^2 = (A_{\alpha_\tau}(\boldsymbol{\theta}, k) + B_{\alpha_\tau}(\boldsymbol{\theta}, k))^2 \frac{k}{N(k\Psi'(k) - 1)} + k\omega^2 f_{k+1}^2 \left(G_k(\alpha_\tau) e^{\mathbf{a}^t \boldsymbol{\theta}} \right).$$

A consistent estimator of σ_d^2 is obtained by replacing $\boldsymbol{\theta}$ and k with their likelihood estimates $\hat{\boldsymbol{\theta}}$ and \hat{k} .

References

- [1] Andrews, L. C. (1985). *Special Functions for Engineers and Applied Mathematicians*. Macmillan, New York.
- [2] Banga, S. J., Patil, G. P., and Taillie, C. (2000a). Likelihood contour method for the calculation of asymptotic upper confidence limits on the risk function for quantitative responses. *Risk Analysis* (under revision).
- [3] Banga, S. J., Patil, G. P., and Taillie, C. (2000b). Sensitivity of normal theory methods to model misspecification in the calculation of upper confidence limits on the risk function for continuous responses. *Environmental and Ecological Statistics*, **7**, 177–189.
- [4] Banga, S. J., Patil, G. P., and Taillie, C. (2000c). Direct calculation of likelihood-based benchmark dose levels for quantitative responses. Technical Report Number 2000–0402, Center for Statistical Ecology and Environmental Statistics, Department of Statistics, Penn State University, University Park, PA.

- [5] Bowman, K. O. and Shenton, L. R. (1988). *Properties of Estimators for the Gamma Distribution*. Marcel Dekker, New York.
- [6] Chen, J. J. and Gaylor, D. W. (1992). Dose response modeling of quantitative response data for risk assessment. *Communications in Statistics—Theory and Methods*, **21(8)**, 2367–2381.
- [7] Crump, K. S. (1984). A new method for determining allowable daily intakes. *Fundamental and Applied Toxicology*, **4**, 854–971.
- [8] Crump, K. S. (1995). Calculation of benchmark doses from continuous data. *Risk Analysis*, **15**, 79–89.
- [9] Crump, K. S. and Howe, R. (1983). A review of methods for calculating confidence intervals in low dose extrapolation. In *Toxicological Risk Assessment*, Clayton, Krewski and Munroe, eds. CRC Press, Boca Raton, FL.
- [10] Gaylor, D. W. and Slikker, W., Jr. (1990). Risk Assessment for Neurotoxic Effects. *Neurotoxicology*, **11**, 211–218.
- [11] Glowa, J. R. (1991). Dose-effect approaches to risk assessment. *Neuroscience and Behavioral Reviews*, **15**, 153–158.
- [12] Kodell, R. L. and West, R. W. (1993). Upper confidence limits on excess risk for quantitative responses. *Risk Analysis*, **13(2)**, 177–182.
- [13] Rao, C. R. (1947). Large sample tests of statistical hypotheses concerning several parameters with applications to problems of estimation. *Proceedings of the Cambridge Philosophical Society*, **44**, 50–57.
- [14] Sciullo, C., Patil, G. P., and Taillie, C. (2000). *Approximate validity of benchmark dose levels obtained by inverting upper confidence bounds on the risk function*. Technical Report Number 2000–0404, Center for Statistical Ecology and Environmental Statistics, Department of Statistics, Penn State University, University Park, PA.
- [15] Stiteler, W. M. and Durkin, P. R. (1990). *Some Statistical Issues Relating to the Characterization of Risk for Toxic Chemicals*. Proceedings of the Workshop on Superfund Hazardous Waste: Statistical Issues in Characterizing a Site: Protocols, Tools, and Research Needs, Arlington, Virginia, February 21–22.
- [16] West, R. W. and Kodell, R. L. (1993). Statistical methods of risk assessment for continuous variables. *Communications in Statistics—Theory and Methods*, **22(12)**, 3363–3376.