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# Direct Calculation of Likelihood-Based Benchmark Dose Levels for Quantitative Responses

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**Abstract.** A benchmark dose (BMD) for quantitative responses is a lower confidence limit on the effective dose corresponding to a specified risk level  $r$ . A commonly adopted method for calculating the BMD is to obtain a pointwise upper confidence curve  $U(d)$  on the risk function and then invert this relationship by solving the equation  $U(d) = r$ . The solution  $d$  is taken to be the BMD. Sciullo *et al.* (2000) have shown that the coverage achieved by this inversion method is at least as great as the coverage achieved by  $U(\cdot)$  but that there is otherwise no general relationship between the two coverage probabilities. The present paper develops a method for direct calculation of the BMD based on the asymptotic distribution of the likelihood ratio statistic. It is further shown that the direct method and the inversion method are equivalent when  $U(\cdot)$  is also based on the likelihood ratio. Since the direct method is known to be asymptotically correct, it follows that the LR-based inversion method is also asymptotically correct. However, the direct method is computationally faster and easier to program. Finally, some simulation studies are conducted to assess the small sample coverage probabilities of the direct method when responses follow either a normal or a gamma distribution.

**Keywords:** BMD; Confidence limits; Dose-response models; Inversion method; Likelihood contour method; Likelihood ratio; Profile likelihood.

## 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 quantitative responses, however, it is usually not apparent how a given response value should be dichotomized into “adverse” or “not adverse.” One solution

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(Chen and Gaylor, 1992; Crump, 1995; Gaylor and Slikker, 1990, 1994; 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. Chen and Gaylor (1992) 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 5<sup>th</sup> 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 under nonlinear transformations of the response.

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.

Based on these ideas, the modeling and risk analysis for quantitative responses is carried out in the following steps (Banga, Patil, and Taillie, 2000a,b,c):

1. First a parametric family  $F(y; \Theta)$  of distribution functions is selected for a continuous response  $y$ . The distributional parameters  $\Theta$  are then modeled as a function,

$$\Theta = \Theta(d, \boldsymbol{\psi}),$$

of the dose  $d$  and some unknown parameters  $\boldsymbol{\psi}$ . The distribution of  $Y(d)$  can then be written as

$$F_d(y) = F(y, \Theta(d, \boldsymbol{\psi})).$$

2. Let  $\tau$  be the abnormal point and  $\alpha_\tau$  the associated control risk. In our approach,  $\alpha_\tau$  is specified by the investigator and then  $\tau$  is determined by the equation

$$\alpha_\tau = F_0(\tau) = F(\tau, \Theta(0, \boldsymbol{\psi})). \tag{1}$$

Note that  $\tau$  is unknown because  $\boldsymbol{\psi}$  is unknown. For a given dose level  $d$ , the total risk function is

$$R(d) = F_d(\tau) = F(\tau, \Theta(d, \boldsymbol{\psi})).$$

Equation (1) can be used to eliminate  $\tau$  so that the risk function is parametrized by  $\boldsymbol{\psi}$ , i.e.,  $R(d) = R(d; \boldsymbol{\psi})$ . The excess or additional risk is defined as  $\pi(d) = R(d) - \alpha_\tau$ . Since  $\alpha_\tau$  is a known constant, one can equivalently work with either  $\pi(d)$  or  $R(d)$ . We generally use  $R(d)$ . The equations in this item apply when the direction of adversity is to the left; the equations have to be modified appropriately if the direction of adversity is to the right.

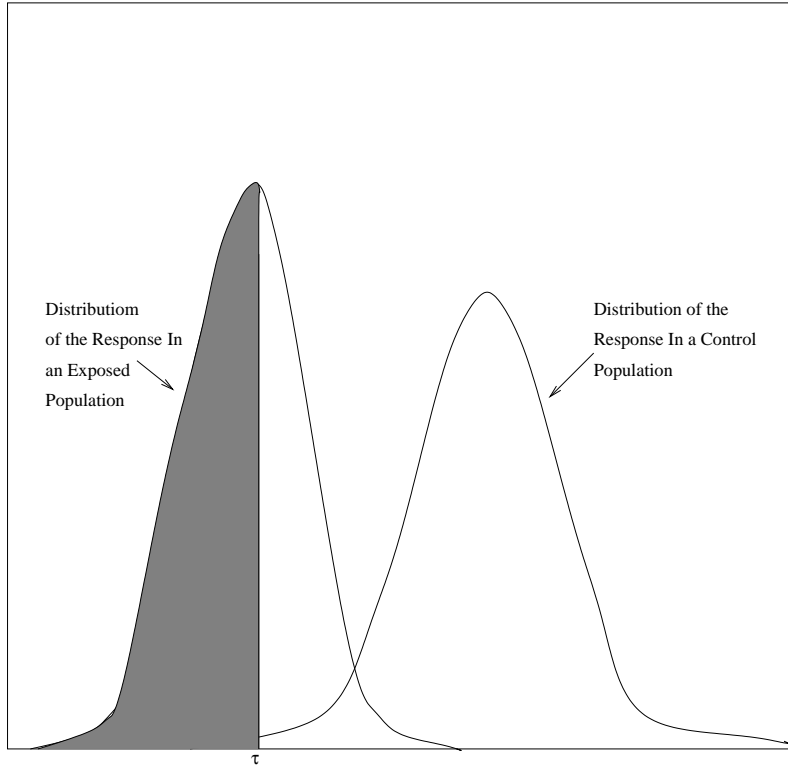


Figure 1: Schematic diagram for defining the abnormal point and corresponding risks. The abnormal point  $\tau$  is a specified quantile of the control population. The shaded tail area of the response distribution for an exposed population represents the risk for that population. The risk for the control population is the background risk and is denoted by  $\alpha_\tau$ . In the approach described here, the value of  $\alpha_\tau$  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  $\tau$  which is unknown.

3. At each dose level  $d$ , an upper confidence limit (UCL) on the risk  $R(d)$  is constructed. These calculations yield a pointwise upper confidence curve  $\widehat{R}_u(d)$  on the risk function. The confidence limit calculations are usually based either upon the asymptotic normality of the maximum likelihood estimates of the parameters in the model or upon the asymptotic distribution of the likelihood ratio statistic (Rao, 1947; Crump and Howe, 1983). The latter method appears to provide more reliable coverage when responses are not normally distributed (Banga, Patil, and Taillie, 2000c).
4. Letting  $\alpha_1$  be any given risk level ( $\alpha_\tau < \alpha_1 < 1$ ), the solution of the equation  $R(d) = \alpha_1$  is the effective dose associated with the risk  $\alpha_1$  and is denoted by  $\eta = \text{ED}_{\alpha_1}$ . See Figure 2. For given  $\alpha_1$ , the effective dose is a scalar function of the parameters in the model, i.e.,  $\eta = \eta(\boldsymbol{\psi})$ . The benchmark dose (BMD) is defined to be a lower confidence limit (LCL) on the effective dose and is denoted by  $\text{BMD}_{\alpha_1}$ .

A traditional method for calculating a benchmark dose is by inverting an upper confidence curve on the risk function (item 3, above). Specifically, if we let  $\widehat{R}_u(d)$  be an upper confidence curve on the risk function, then the solution of the equation  $\widehat{R}_u(d) = \alpha_1$  is taken to be a  $\text{BMD}_{\alpha_1}$ . Sciullo, Patil, and Taillie (2000) have made a detailed study of the coverage probabilities achieved by this inversion method and have reached the following conclusions:

1. The coverage achieved by the inversion-based BMD is at least as great as the coverage achieved by the upper confidence curve  $\widehat{R}_u(d)$ . The inversion method is therefore conservative.
2. The coverage achieved by the inversion-based BMD equals the coverage achieved by the upper confidence curve provided the upper confidence curve  $\widehat{R}_u(d)$  is monotone increasing (beyond some possible initial dip) *with probability one*. However, this is a very severe requirement on the dose-response model and on the method used for obtaining the upper confidence curve. This requirement is shown to be satisfied for normally distributed responses whose mean is a *linear* function of the dose and where the (exact) noncentral- $t$  method (Gaylor and Slikker, 1990; Kodell and West, 1993) is used to obtain the upper confidence curve.
3. The requirement of item 2 is not satisfied for normally distributed responses whose mean is a *quadratic* function of the dose and where the noncentral- $t$  method is used to obtain the upper confidence curve. Instead, depending upon the model parameters, the coverage achieved by the inversion-based BMD can take any value between the nominal coverage probability and 100 percent. For fixed model parameters, however, the inversion method is asymptotically correct in the sense that achieved coverage converges to nominal coverage with increasing sample size.

The purpose of the present paper is two-fold: (i) we develop a direct method for calculating a BMD based on the asymptotic distribution of the likelihood ratio statistic which gives correct coverage asymptotically and (ii) we show that this direct BMD is identical to the inversion-based BMD (for all sample sizes) when the upper confidence curve on the risk is also based on the likelihood ratio statistic. This allows us to conclude that the LR-based inversion method provides asymptotically correct coverage probabilities.

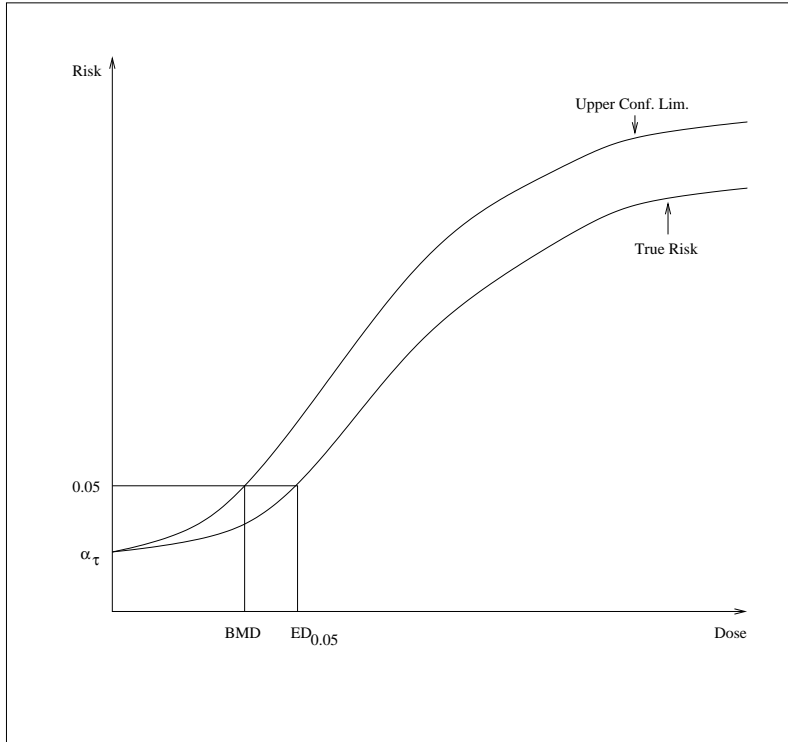


Figure 2: Simple illustration of the calculation of the BMD. The control or background risk  $\alpha_\tau$  is the risk at dose level  $d = 0$ . Next, the investigator must specify an “acceptable” risk level  $\alpha_1 > \alpha_\tau$ . The picture illustrates with  $\alpha_1 = 0.05$ . Inversion of the (unknown) true risk function would yield the effective dose,  $\eta = ED_{\alpha_1}$ . The BMD is a lower confidence limit on the effective dose. Inversion of a calculated upper confidence curve on the risk function is a traditional method for obtaining a BMD. However, Sciullo, Patil, and Taillie (2000) have shown that the inversion method results in correct coverage probability only under severe restrictions on the model and the method used to obtain the upper confidence curve. The present paper proposes a direct LR-based calculation of the BMD.

## 2 LR-Based Confidence Limits on Scalar Parameters

Consider a statistical model parametrized by a  $q$ -dimensional vector of parameters  $\boldsymbol{\psi} = (\psi_1, \dots, \psi_q)^t$ . Our interest lies in obtaining one-sided confidence limits on a scalar-valued function

$$\varphi = \varphi(\boldsymbol{\psi})$$

of the parameters. Although the discussion in this section is general, the two cases of interest for the present paper are: (i)  $\varphi$  is the risk  $R(d; \boldsymbol{\psi})$  for a given dose level  $d$  and we want an upper confidence limit  $\hat{R}_u(d)$  on this risk and (ii)  $\varphi$  is an effective dose  $\eta = \text{ED}_{\alpha_1}$  for specified  $\alpha_1$  and we seek a lower confidence limit on  $\eta$  (i.e., a benchmark dose).

Banga, Patil, and Taillie (2000a,c) have formulated a computationally convenient form of the profile likelihood method (Lindsey, 1996, chaps. 3 and 5) for calculating asymptotic confidence limits on scalar parameters such as  $\varphi(\boldsymbol{\psi})$ . Let

- $L(\boldsymbol{\psi})$  be the likelihood function for the model,
- $l(\boldsymbol{\psi}) = -\log L(\boldsymbol{\psi})$ , and
- $\mathcal{D}(\boldsymbol{\psi}) = 2(l(\boldsymbol{\psi}) - l(\hat{\boldsymbol{\psi}})) = -2 \log \left( \frac{L(\boldsymbol{\psi})}{L(\hat{\boldsymbol{\psi}})} \right)$ , where  $\hat{\boldsymbol{\psi}}$  is the MLE of  $\boldsymbol{\psi}$ .

If  $\tilde{\boldsymbol{\psi}}$  is the MLE of  $\boldsymbol{\psi}$  under some null hypothesis (sub-model), then  $\mathcal{D}(\tilde{\boldsymbol{\psi}})$  is the likelihood ratio test statistic.

**Theorem 1 (Likelihood ratio confidence intervals)** *An asymptotic 100(1 -  $\alpha$ )% one-sided UCL for  $\varphi$  is the maximum  $\varphi_u$  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  $\varphi$  is the minimum  $\varphi_l$  of  $\varphi(\boldsymbol{\psi})$  subject to  $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2$  (see Figure 3).*

As indicated in Figure 3, the task of finding one-sided confidence limits on  $\varphi$  has a simple geometric interpretation. The extrema occur where the parameter contours  $\varphi = c$  are tangent to the deviance contour  $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2$ . Equivalently, this amounts to finding a scalar  $c$  such that the vector perpendicular to the contour  $\varphi = c$  is parallel to the vector perpendicular to the contour  $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2$ . This is essentially the geometrical interpretation of the Lagrange multiplier method for the problem of optimizing  $\varphi(\boldsymbol{\psi})$  subject to the constraint  $\mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2$ .

The Lagrange multiplier equations for the optimization problem are given by

$$\begin{cases} E_0 : \mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2 \\ E_1, \dots, E_q : \frac{\partial}{\partial \psi_i} \mathcal{D}(\boldsymbol{\psi}) - \lambda \frac{\partial}{\partial \psi_i} \varphi(\boldsymbol{\psi}) = 0, \quad i = 1, \dots, q, \end{cases}$$

where  $\lambda$  is the Lagrange multiplier. A vector representation of equations  $E_1, \dots, E_q$  is

$$\nabla \mathcal{D}(\boldsymbol{\psi}) = \lambda \nabla \varphi(\boldsymbol{\psi}).$$

The gradient  $\nabla \varphi$  points in the direction of increasing  $\varphi$  while  $\nabla \mathcal{D}$  points to the exterior of the region bounded by the  $\mathcal{D}$ -contours. Referring to Figure 3, this means that the solution,

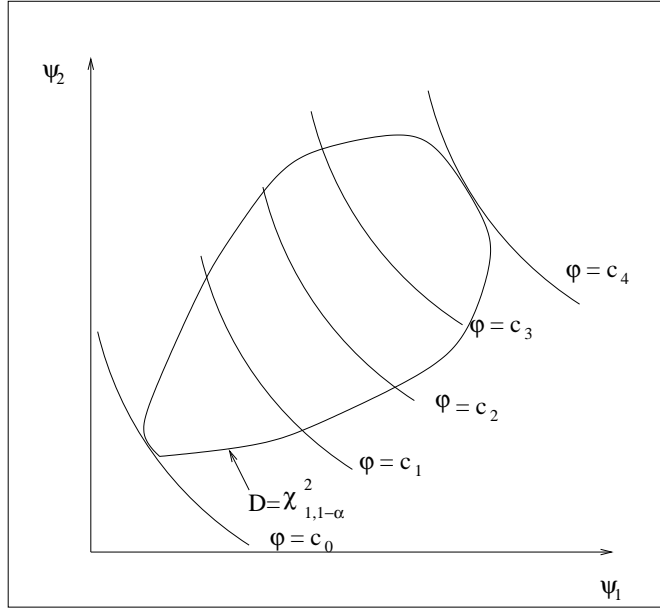


Figure 3: Two-dimensional schematic for LR-based confidence intervals for a scalar parameter  $\varphi$ . The constants  $c_0 < c_1 < c_2 < c_3 < c_4$  label various contours of  $\varphi$ . A one-sided UCL for  $\varphi$  is  $\varphi = c_4$  which is obtained by maximizing  $\varphi$  along the contour  $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$ . Similarly,  $c_0$  is an LCL for  $\varphi$  obtained by minimizing  $\varphi$  along the contour  $\mathcal{D}(\boldsymbol{\psi}) = \chi^2_{1,1-2\alpha}$ .

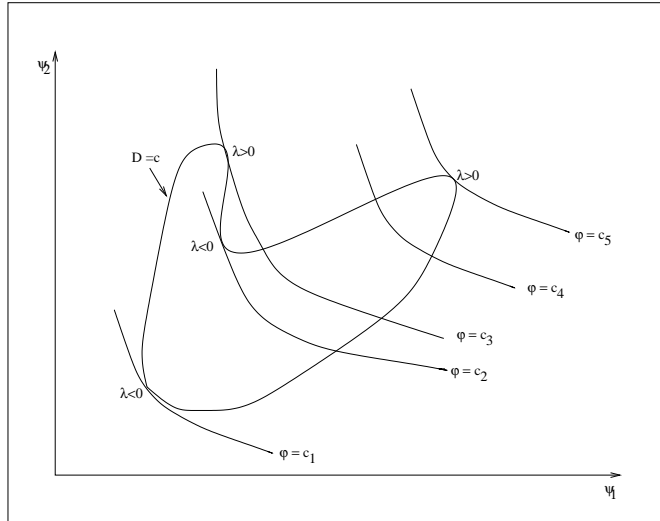


Figure 4: Two-dimensional illustration of how  $\varphi$  can be multi-modal along a deviance contour. In this example,  $c_1$  and  $c_5$  are respectively the global minimum and maximum, whereas  $c_2$  and  $c_3$  are respectively local minimum and maximum.

$\boldsymbol{\psi}^*$ , which yields an upper confidence limit for  $\varphi(\boldsymbol{\psi})$  is associated with a positive  $\lambda$ . On the other hand, when a lower confidence limit is obtained, the associated  $\lambda$  is negative.

Multi-modality problems may be encountered along the contour  $\mathcal{D}(\boldsymbol{\psi}) = \text{constant}$  even if the likelihood surface is well behaved, i.e., unimodal. See Figure 4.

## 2.1 Algorithms for solving the Lagrange equations

Consider the following augmented system of Lagrange equations:

$$\begin{cases} E_0 : \mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2 \\ E_1, \dots, E_q : \frac{\partial}{\partial \psi_i} \mathcal{D}(\boldsymbol{\psi}) - \lambda \frac{\partial}{\partial \psi_i} \varphi(\boldsymbol{\psi}) = 0, & i = 1, \dots, q \\ E_{q+1} : \varphi(\boldsymbol{\psi}) = c. \end{cases} \quad (2)$$

We describe two ways of solving these equations to obtain an asymptotic  $100(1 - \alpha)\%$  UCL for  $\varphi(\boldsymbol{\psi})$ . Computation of an LCL is analogous.

1. **Parameter Contour Method (PCM).** We start this algorithm by fixing a value for  $c$ . Next, we solve simultaneously the equations  $E_1, \dots, E_{q+1}$  for  $(\boldsymbol{\psi}, \lambda)$  to obtain a solution  $\boldsymbol{\psi}^*$ . The search is constrained to the parameter contour defined by equation  $E_{q+1}$ . Note that  $\mathcal{D}(\boldsymbol{\psi}^*)$  is the normed profile likelihood (Lindsey, 1996, p. 111) for the parameter  $\varphi$ , evaluated at  $\varphi = c$ . We then keep adjusting  $c$  until the solution  $\boldsymbol{\psi}^*$  satisfies equation  $E_0$ . The value of  $c$  for which  $\boldsymbol{\psi}^*$  satisfies  $E_0$  is then taken to be the upper confidence limit on  $\varphi$ .
2. **Likelihood Contour Method (LCM).** This method consists of solving the equations  $E_0, E_1, \dots, E_q$  for  $(\boldsymbol{\psi}, \lambda)$  to obtain the global maximum  $\boldsymbol{\psi}^*$ . The UCL  $\varphi_u = c$  is then found as  $c = \varphi(\boldsymbol{\psi}^*)$  from the equation  $E_{q+1}$ . In this method, the search is constrained to the likelihood contour defined by equation  $E_0$ .

The two methods are clearly equivalent. The LCM version is more convenient to program but its convergence relies heavily on the choice of starting value, particularly the starting value for  $\lambda$ . The PCM method, on the other hand, is a step by step procedure and does not depend so much upon the starting values. However, one will need to adjust the value of  $c$  appropriately to move toward the desired solution which depends on whether an upper or lower confidence limit is sought. Consequently, the PCM algorithm can be inconvenient to program particularly in settings such as simulation where there is a need for automatic computation.

## 2.2 Starting values: Asymptotic solutions of the LCM equations

Banga, Patil, and Taillie (2000a) have obtained highly accurate starting values for solving the LCM equations  $E_0, E_1, \dots, E_q$ . The idea is to approximate these equations by using the lowest order terms in their asymptotic expansions. The resulting equations can be solved explicitly. These approximate solutions can be used directly as the confidence limit if the resulting loss of accuracy is acceptable or they can be used as starting values in an iterative solution of the exact LCM equations.

**Theorem 2** *The lowest order terms in the asymptotic expansions of the LCM equations  $E_0, E_1, \dots, E_q$  have exactly two solutions  $(\boldsymbol{\psi}_\pm, \lambda_\pm)$  given by*

$$\boldsymbol{\psi}_\pm = \hat{\boldsymbol{\psi}} + \frac{\lambda_\pm}{2} H^{-1}(\hat{\boldsymbol{\psi}}) \nabla \varphi(\hat{\boldsymbol{\psi}})$$

$$\frac{\lambda_\pm}{2} = \pm \frac{\sqrt{\chi_{1, 1-2\alpha}^2}}{\sqrt{[\nabla \varphi(\hat{\boldsymbol{\psi}})]^t H^{-1}(\hat{\boldsymbol{\psi}}) \nabla \varphi(\hat{\boldsymbol{\psi}})}},$$

where  $H(\boldsymbol{\psi})$  is the total negative Hessian matrix of the model. The positive sign corresponds to the UCL and the negative sign to the LCL. In these formulae, the negative Hessian matrix can be replaced by the information matrix to which it is asymptotically equivalent.

The approximate solution  $(\boldsymbol{\psi}_\pm, \lambda_\pm)$  is used as starting value for iterative solution of the LCM equations;  $(\boldsymbol{\psi}_\pm, \lambda_\pm)$  is usually so close to the exact solution that only a few iterations are required. Alternatively,  $\varphi(\boldsymbol{\psi}_+)$  and  $\varphi(\boldsymbol{\psi}_-)$  can be used as approximate upper and lower confidence limits on  $\varphi$ .

### 3 Equivalence of LR-Based Direct and Inverse Methods

In this section, we show that the direct and inverse methods yield exactly the same BMD value provided the LR confidence limits of Theorem 1 are used throughout. We begin by specializing the augmented Lagrange equations (2) to the problem at hand.

#### 3.1 Augmented Lagrange equations for direct calculation of BMD

For directly calculating a BMD, the parameter of interest is the effective dose so that  $\varphi = \eta(\boldsymbol{\psi}) = \text{ED}_{\alpha_1}$ . The equation  $E_{q+1}$  becomes

$$\eta(\boldsymbol{\psi}) = d, \tag{3}$$

where we are using  $d$  instead of  $c$  on the right because  $\eta$  is a dose level. But  $\eta(\boldsymbol{\psi}) = \text{ED}_{\alpha_1}$  is defined implicitly as the solution  $d'$  of the equation  $R(d'; \boldsymbol{\psi}) = \alpha_1$ , so that equation (3) is equivalent to

$$R(d; \boldsymbol{\psi}) = \alpha_1. \tag{4}$$

For equations  $E_1, \dots, E_q$ , we need the partial derivatives  $\frac{\partial \eta}{\partial \psi_i}$ . These can be obtained by differentiating

$$R(\eta(\boldsymbol{\psi}); \boldsymbol{\psi}) = \alpha_1 \tag{5}$$

to obtain

$$\frac{\partial \eta}{\partial \psi_i} = -\frac{\frac{\partial R}{\partial \psi_i}}{\frac{\partial R}{\partial d}}. \tag{6}$$

Putting all this together, the augmented Lagrange equations (2) for computing a BMD directly become

$$\begin{cases} E_0 : \mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2 \\ E_1, \dots, E_q : \frac{\partial}{\partial \psi_i} \mathcal{D} + \lambda \frac{\frac{\partial R}{\partial \psi_i}}{\frac{\partial R}{\partial d}} = 0, & i = 1, \dots, q \\ E_{q+1} : R(d; \boldsymbol{\psi}) = \alpha_1, \end{cases} \quad (7)$$

where  $\alpha_1$  is fixed. Given  $\alpha_1$ , this system of equations generally has multiple solutions  $(d, \boldsymbol{\psi}, \lambda)$ ; the values of  $d$  corresponding to the various solutions will be referred to as **LR candidate values** for the benchmark dose. The smallest of these candidate values is the  $\text{BMD}_{\alpha_1}$  as calculated by the direct LR method. From general properties of the LR statistic (subject to regularity conditions), we know that the direct method yields an asymptotically valid BMD.

### 3.2 Augmented Lagrange equations for UCL on the risk

Calculating a BMD using the inversion approach is performed in two steps. First, a pointwise  $100(1 - \alpha)\%$  upper confidence curve  $\widehat{R}_u(d)$  on the risk function  $R(d)$  is constructed. Second, the equation

$$\widehat{R}_u(d) = \alpha_1 \quad (8)$$

is solved and the smallest possible solution  $d$  is taken to be the  $\text{BMD}_{\alpha_1}$  value. We suppose that Theorem 1 is used to obtain the upper confidence limit on the risk for each fixed dose level  $d$ . Here, the parameter of interest is  $\varphi = R(d; \boldsymbol{\psi})$  and augmented Lagrange equations (2) become

$$\begin{cases} E_0 : \mathcal{D}(\boldsymbol{\psi}) = \chi_{1,1-2\alpha}^2 \\ E_1, \dots, E_q : \frac{\partial}{\partial \psi_i} \mathcal{D} - \xi \frac{\partial R}{\partial \psi_i} = 0, & i = 1, \dots, q \\ E_{q+1} : R(d; \boldsymbol{\psi}) = \alpha_1, \end{cases} \quad (9)$$

where we have used  $\xi$  for the Lagrange multiplier to avoid confusion with the  $\lambda$  in the system (7). We have also used  $\alpha_1$  instead of  $c$  on the right hand side of equation  $E_{q+1}$  to emphasize the parallel with the system (7).

### 3.3 Comparison of direct and inverse methods

The two systems of equations (7) and (9) are the link between lower confidence limits on the effective dose and upper confidence limits on the risk. In the system (7), the risk level  $\alpha_1$  is held fixed and the smallest  $d$  occurring among solutions is the LCL on  $\text{ED}_{\alpha_1}$ . In the system (9), the dose level  $d$  is held fixed and the largest value of  $\alpha_1$  occurring among the solutions is the UCL on the risk at dose level  $d$ . This latter UCL is what we denote by  $\widehat{R}_u(d)$ .

We suppose that the following regularity conditions are satisfied: (i)  $\widehat{R}_u(d)$  is a continuous function of  $d$  for  $d \geq 0$  and (ii)  $\widehat{R}_u(0) = \alpha_\tau$ . These conditions are satisfied for most benchmark dose-response models including the homoscedastic normal model, the gamma model, the reciprocal gamma model, and the lognormal model. The rationale for condition (ii) is that the true risk  $R(0)$  at  $d = 0$  is the *known* value  $\alpha_\tau$ .

**Theorem 3** *Let  $\alpha_1 > \alpha_\tau$  and suppose the above regularity conditions are satisfied. Then*

- (a) *If  $d$  is a solution of  $\hat{R}_u(d) = \alpha_1$ , then  $d$  is an LR candidate value for the benchmark dose at level  $\alpha_1$ , i.e.,  $d$  occurs among the solutions of (7).*
- (b) *If  $d$  is a LR candidate value for the benchmark dose at level  $\alpha_1$ , then there is a dose level  $d^*$  such that  $0 < d^* \leq d$  and  $\hat{R}_u(d^*) = \alpha_1$ .*

**Proof.** First we consider part (a). If  $\hat{R}_u(d) = \alpha_1$ , then there is a solution  $(\alpha_1, \boldsymbol{\psi}, \xi)$  to the system (9). Then  $(d, \boldsymbol{\psi}, \lambda)$  with  $\lambda = -\xi \partial R(d; \boldsymbol{\psi}) / \partial d$  is a solution to the system (7) so that  $d$  is an LR candidate value for  $\text{BMD}_{\alpha_1}$ . Next, we consider part (b). If  $d$  is an LR candidate value for  $\text{BMD}_{\alpha_1}$ , then the system (7) has a solution of the form  $(d, \boldsymbol{\psi}, \lambda)$  and the system (9) has the corresponding solution  $(\alpha_1, \boldsymbol{\psi}, \xi)$  where  $\xi$  satisfies  $\lambda = -\xi \partial R(d; \boldsymbol{\psi}) / \partial d$ . Since  $\hat{R}_u(d)$  is the largest value of  $\alpha_1$  occurring in such solutions, it follows that  $\hat{R}_u(d) \geq \alpha_1$ . Regularity conditions (i) and (ii) and the intermediate value theorem imply that there is a  $d^*$  with  $0 < d^* \leq d$  and  $\hat{R}_u(d^*) = \alpha_1$ . This completes the proof.

**Corollary 1 (Equivalence of direct and inverse methods)** *Let  $\alpha_1 > \alpha_\tau$ . The smallest solution of the equation  $\hat{R}_u(d) = \alpha_1$  is also the smallest LR candidate value for the benchmark dose  $\text{BMD}_{\alpha_1}$ . In other words, the smallest solution of the equation  $\hat{R}_u(d) = \alpha_1$  coincides with the benchmark dose  $\text{BMD}_{\alpha_1}$  as determined by the direct LR method.*

**Corollary 2 (Asymptotic validity of LR-based inversion method)** *Let  $\alpha_1 > \alpha_\tau$  and let  $\hat{d}$  be the smallest solution of the equation  $\hat{R}_u(d) = \alpha_1$ . As an LCL on the effective dose,  $\hat{d}$  has correct asymptotic coverage  $1 - \alpha$ .*

It must be emphasized that the coverage asserted in the preceding corollary is asymptotic. In addition,  $\hat{d}$  has correct asymptotic coverage because it coincides with the direct LR determination of the BMD and not because  $\hat{R}_u(d)$  has the correct asymptotic coverage of the true risk. As already pointed out, Sciullo, Patil, and Taillie (2000) have shown that, in general, there is no relationship between the small sample coverage of  $\hat{d}$  and the small sample coverage of  $\hat{R}_u(d)$ .

## 4 Starting Values for Direct Determination of BMD

As long as LR methods are employed, one can use either the direct or the inverse method for obtaining the BMD. Since the direct method can be computationally simpler, we provide some details on obtaining starting values. There are actually, two possibilities here. First, one can simply specialize Theorem 2 to the case at hand.

**Theorem 4** *The starting value given by Theorem 2 for direct determination of a LCL on the effective dose  $\eta$  is  $(\boldsymbol{\psi}_-, \lambda_-)$  where*

$$\boldsymbol{\psi}_- = \hat{\boldsymbol{\psi}} + \frac{\lambda_-/2}{\left. \frac{\partial R(d; \hat{\boldsymbol{\psi}})}{\partial d} \right|_{d=\hat{\eta}}} H^{-1}(\hat{\boldsymbol{\psi}}) \nabla R(\hat{\eta}, \hat{\boldsymbol{\psi}}) \quad (10)$$

and

$$\frac{\lambda_-}{2} = - \left| \frac{\partial R(d; \hat{\boldsymbol{\psi}})}{\partial d} \right|_{d=\hat{\eta}} \left| \frac{\sqrt{\chi_{1, 1-2\alpha}^2}}{\sqrt{[\nabla R(\hat{\eta}; \hat{\boldsymbol{\psi}})]^t H^{-1}(\hat{\boldsymbol{\psi}}) \nabla R(\hat{\eta}; \hat{\boldsymbol{\psi}})}} \right|, \quad (11)$$

where  $\hat{\eta}$  is the MLE of the effective dose  $\eta$ , i.e., the solution  $d'$  of the equation  $R(d'; \hat{\boldsymbol{\psi}}) = \alpha_1$ .

This follows easily from Theorem 2 using equation (6). A limitation of this approach is that it relies on the MLE  $\hat{\eta}$  of the effective dose which is the solution  $d'$  of the equation  $R(d'; \hat{\boldsymbol{\psi}}) = \alpha_1$ . In rare instances, depending upon the value of  $\alpha_1$  and the estimate  $\hat{\boldsymbol{\psi}}$ , the estimated risk function  $R(d'; \hat{\boldsymbol{\psi}})$  may fail to approach unity as  $d'$  becomes large and the equation  $R(d'; \hat{\boldsymbol{\psi}}) = \alpha_1$  may not have a solution. In such a case, this method cannot be used to obtain a starting value for the BMD determination. In an actual data analysis, one would probably look for a different model, but such an option is not available in a simulation study.

An alternative approach uses Theorem 2 to obtain starting values for the upper confidence curve and then inverts this curve to obtain the needed starting value for direct calculation of the BMD. According to Theorem 2, a starting value for obtaining the upper confidence curve on the risk at dose level  $d$  is

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

The smallest solution  $d'$  of the equation  $R(d'; \boldsymbol{\psi}_-(d')) = \alpha_1$  is therefore an approximate BMD value and we use this value in Theorem 4 instead of  $\hat{\eta}$  to obtain our starting value. This was found to work reliably in all our simulations.

## 5 Simulation Study

We have conducted a simulation study to assess the small sample coverage achieved by the direct method for determining the BMD. Coverages have been obtained for BMD values using the full iterative solution of the Lagrange equations and also using only the starting values (approximation method). Two distributional models are considered: the homoscedastic normal model and the gamma model. Details of the likelihood equations for these models are given in Banga, Patil, and Taillie (2000a,c) and are not repeated here. In all cases, the direction of adversity is to the left.

### 5.1 Study I: Homoscedastic normal model

Responses follow a homoscedastic normal distribution with variance  $\sigma^2$  and whose mean is a quadratic function of the dose. Specifically, the response is

$$\begin{aligned} y(d) &= \mu(d) + \epsilon \\ &= 3 - d - 0.1 d^2 + \epsilon, \end{aligned}$$

where  $\epsilon$  is generated as  $N(0, \sigma^2)$  and  $\sigma$  is fixed at one of the six values 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0. For each of these six sets of model parameters, 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 values of  $\sigma$ . With this setup, experiment-to-experiment differences can be attributed to distributional changes as the parameter  $\sigma$  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% LCLs are calculated in each of the 3 sample sizes of the 6 experiments for 4000 replicates. The estimated coverage probability in each case is computed as the proportion of the 4000 replications for which the resulting LCLs are less than or equal to the true effective dose  $ED_{0.1}$ . 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. Figure 5 summarizes the achieved coverages. The direct method consistently gives over-coverage which goes to zero rather slowly with increasing  $N$ . Interestingly, coverages for the approximation method are closer to the nominal 95 percent level, although this advantage gradually disappears with increasing  $N$ .

## 5.2 Study II: Gamma model

Here, the responses follow a gamma distribution in which the shape parameter  $k$  is unknown but does not depend upon the dose and the log of the mean is a quadratic function of the dose. Specifically,

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

where the parameter  $k$  is fixed at one of the six values 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0. The direction of adversity is to the left. Other features of this study are the same as Study I. Figure 6 summarizes the achieved coverages. Here the direct method gives under-coverage for small sample sizes ( $N = 25$ ) but coverage quickly approaches nominal levels with increasing  $N$ . The approximate method gives poorer coverage than the direct method. Accordingly, with gamma distributed responses it is worthwhile to do at least several iterations of the Lagrange equations, particularly when the sample sizes are small (less than 50 or 100, say).

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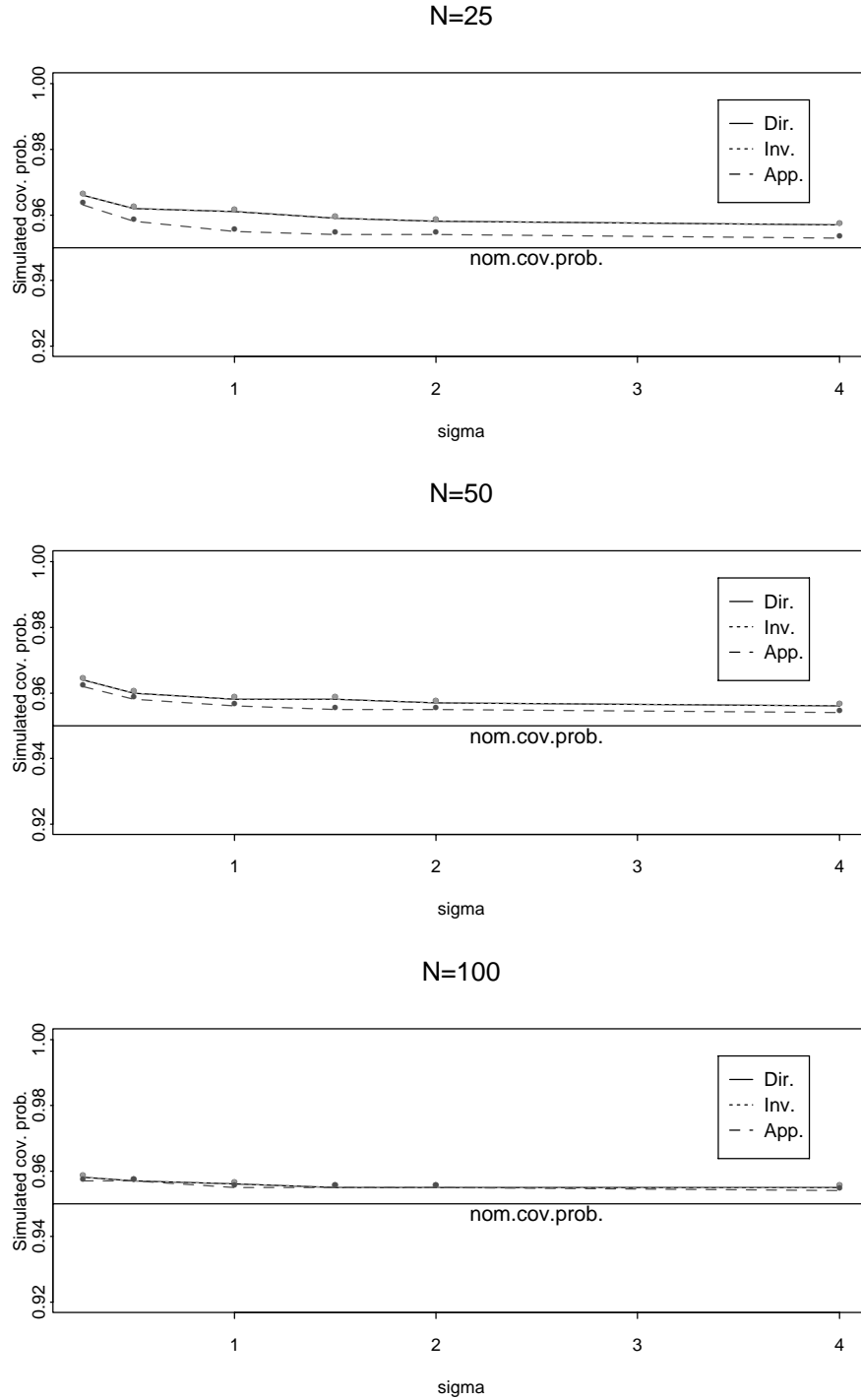


Figure 5: Study I: Simulated coverage probabilities for BMD values calculated for homoscedastic normally distributed responses with standard deviation  $\sigma$  and with a mean that is a quadratic function of the dose level. The direct (Dir.) and inverse (Inv.) methods yield identical BMD values. The approximate method (App.) uses the starting values as approximate BMD values. The targeted coverage probability is 0.95. The achieved coverage probabilities are obtained for each of 3 sample sizes:  $N = 25$ ,  $50$  and  $100$ . The simulation error has a standard deviation of about 0.003.

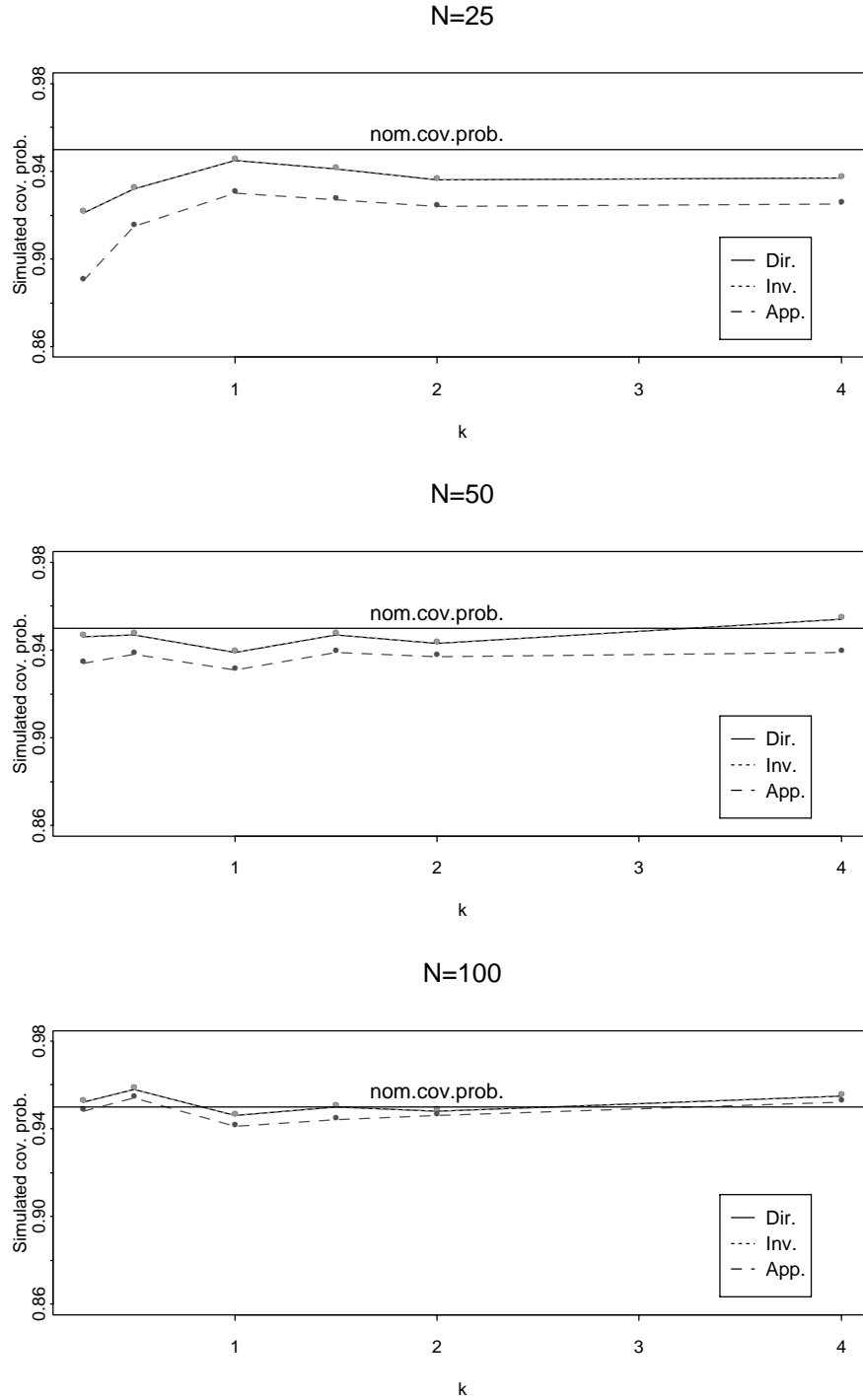


Figure 6: Study II: Simulated coverage probabilities for BMD values calculated for gamma distributed responses with shape parameter  $k$  and with the log of the mean as a quadratic function of the dose level. The direct (Dir.) and inverse (Inv.) methods yield identical BMD values. The approximate method (App.) uses the starting values as approximate BMD values. The targeted coverage probability is 0.95. The achieved coverage probabilities are obtained for each of 3 sample sizes:  $N = 25$ ,  $50$  and  $100$ . The simulation error has a standard deviation of about 0.003.

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