

# A Newton-Based Approach for Attributing Tumor Lethality in Animal Carcinogenicity Studies\*

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## **Abstract**

A new Newton-based approach is proposed for finding the global maximum of a nonlinear function subject to various inequality constraints. This method can be applied to nonparametric maximum likelihood estimation problems to attribute tumor lethality in long-term carcinogenicity studies. This method is substantially faster and easier to implement than the Complex Method used in Ahn, Kodell and Moon (Applied Statistics, 2000). This approach is very useful especially when there exist a large number of parameters of interest to be estimated and many nonlinear inequality constraints. A Monte Carlo simulation study is conducted to evaluate the computational efficiency and accuracy of the estimates obtained from the new approach. The advantages of using the Newton-based approach are illustrated with a real data set.

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\* *Key words:* Cause of death, Inequality constraint, Maximum likelihood, Optimization, Sacrifice

# 1 Introduction

Animal carcinogenicity experiments are employed to test the carcinogenic potential of drugs and other chemical substances. A statistical test proposed by Peto et al. (1980) is widely used and recommended by the International Agency for Research on Cancer (IARC) for analyzing tumor data from such studies. This test requires information on cause of death (COD) or context of observation provided by pathologists. However, COD information is often unavailable, and even when it is available, the cause-of-death/context-of-observation assignment is often recognized to be prone to error (Kodell et al., 1982; Lagakos and Ryan, 1985; Archer and Ryan, 1989).

Recently, Ahn, Kodell and Moon (2000) developed a nonparametric maximum likelihood estimation (NPMLE) method for attributing tumor lethality of occult tumors in the absence of COD information. Imputed numbers of fatal and incidental tumors provided by the method of Ahn et al. may be used in place of pathologist-assigned COD data to implement the Peto test. In the maximum likelihood estimation, Ahn et al. proposed a direct-search algorithm using a mixture likelihood on fatal and incidental tumors. The maximization of the nonlinear likelihood function involves both implicit and explicit inequality constraints of various parameters of a nonlinear function. The Complex Method (Box, 1965) was used by Ahn et al. for the problem of constrained maximization. Although this optimization method guarantees obtaining the global maximum, it is difficult to program and extremely slow.

In this paper, a Newton-based approach is proposed to find the constrained maximum likelihood estimates. The proposed method is easy to implement and substantially faster than the Complex Method. Computing time for 5000 simulation data sets in this study was less than 4 minutes on a Sun Ultra Sparc 60 workstation with the Newton-based method. It took approximately 5 days for the same data sets with the Complex Method.

Consider a nonlinear system of algebraic equations as

$$H(\mathbf{x}) = 0, \tag{1}$$

where  $H : R^n \rightarrow R^n$ . Solving (1) for  $\mathbf{x}$  is a classical problem with applications in many areas of engineering. Newton's (see Blum et al., 1997) and Broyden's (1965) methods are the two most

popular methods for finding the solution of (1).

Newton's method defined as

$$N_H(\mathbf{x}) = \mathbf{x} - [H'(\mathbf{x})]^{-1} H(\mathbf{x})$$

is an iteration method based on the map from  $R^n$  to itself, where  $H'(\mathbf{x})$  is the derivative of  $H$  at  $\mathbf{x}$ . Convergence of Newton's method has been an important issue since Newton's method provides a basis for numerical methods for solving nonlinear algebraic equations. It is also known for a fast convergence rate.

Suppose there exist  $\mathbf{r} \in R^n$ ,  $\gamma > 0$  and  $\omega > 0$  such that  $N(\mathbf{r}, \gamma) \subset D \subset R^n$ ,  $H(\mathbf{r}) = 0$  and  $H'(\mathbf{r})^{-1}$  exists with  $\| H'(\mathbf{r})^{-1} \| < \omega$ , where  $N(\mathbf{r}, \gamma)$  is an open neighborhood of  $\mathbf{r}$  and  $D$  in the domain of contraction. Here,  $H$  is assumed to be continuously differentiable, and  $H'$  is Lipschitz continuous in the open neighborhood. Then Newton's method converges quadratically if an initial guess  $\mathbf{x}_0$  is in the neighborhood  $N(\mathbf{r}, \gamma)$  of a root  $\mathbf{r} \in R^n$ . Broyden's method is popular when the derivative of  $H$  is not available or expensive to compute. The approximation to the derivative of  $H(\mathbf{x})$  is updated at each iteration.

In this paper, we propose a Newton-based NPMLE method for attributing tumor lethality, where the log-likelihood function is an analytic function and its derivatives are not difficult to compute. Because the likelihood function is constrained by both explicit bounds on the parameters and implicit nonlinear inequality constraints, modifications of the commonly used Newton's method for unconstrained problems must be made. Data with only a single terminal sacrifice are considered in this study since most of the animal carcinogenicity studies are designed with a single terminal sacrifice. However, our method can analyze both multiple-sacrifice and single-sacrifice data.

The Complex Method has been implemented in C and the Newton-based method has been implemented in Fortran. The program for the Complex Method can be obtained from the Applied Statistics RSS/Blackwells website and the Newton-based method can be obtained from the authors.

## 2 Nonparametric Maximum Likelihood Estimation

The maximum likelihood estimation method proposed by Ahn et al. (2000) is outlined in this section. Consider an experiment with a control and  $g - 1$  dose groups. Let  $0 = t_0 < t_1 < \dots < t_m$  be  $m$  appropriately spaced sacrifice intervals with sacrifices at  $t_1, \dots, t_m$ , where  $t_m$  denotes terminal sacrifice time. Divide the time scale into discrete intervals with the  $j$ th interval  $I_j = (t_{j-1}, t_j]$ ,  $j = 1, \dots, m$ .

Define  $d_{ij}$ ,  $a_{1ij}$ ,  $b_{1ij}$ ,  $a_{2ij}$ , and  $b_{2ij}$  as the numbers of natural deaths from fatal tumor, natural deaths with incidental tumor, natural deaths without tumor, sacrifices with tumor, and sacrifices without tumor, respectively, within the  $j$ th interval of the  $i$ th dose group. In the discussion of the estimation, the subscript  $i$  will be suppressed since the estimation is performed separately for each group. Let  $T_1$ ,  $T_D$ , and  $X_C$  be random variables representing time to onset of the tumor of interest, the overall time to death from the tumor of interest, and time to death from a cause other than the tumor of interest, respectively. Assume that  $T_1$  and  $T_D$  are independent of  $X_C$ . Define the survival function for the distribution of time to tumor onset,  $S(t)$ , as  $\Pr(T_1 > t)$ , the survival function with respect to death caused by the tumor of interest,  $P(t)$ , as  $\Pr(T_D > t)$ , and the survival function with respect to death from competing risks,  $Q(t)$ , as  $\Pr(X_C > t)$ .

Define  $\pi_j = S(t_j)/P(t_j)$ ,  $p_j = P(t_j)/P(t_{j-1})$ , and  $q_j = Q(t_j)/Q(t_{j-1})$  for  $j = 1, \dots, m$ . Then the survival functions can be expressed as

$$P(t_j) = \prod_{k=1}^j p_k, \quad Q(t_j) = \prod_{k=1}^j q_k \quad \text{and} \quad S(t_j) = \pi_j P(t_j), \quad j = 1, \dots, m.$$

These reparameterized survival functions may be used to estimate distributions of the time-to-onset-of and time-to-death-from tumors of interest. The first explicit constraint,  $0 \leq \pi_j \leq 1$ , is derived due to the fact that  $T_1 < T_D$  implies  $S(t_j)$  does not exceed  $P(t_j)$ . The monotonicity of  $P(t)$  and  $Q(t)$  implies the other explicit constraints,  $0 \leq p_j \leq 1$  and  $0 \leq q_j \leq 1$ , respectively. The monotonicity of  $S(t)$  gives the implicit constraint  $\pi_j p_j \leq \pi_{j-1}$ .

The log-likelihood function for the parameters  $\pi_j$ ,  $p_j$ , and  $q_j$  was derived in Ahn et al. (2000)

as

$$\begin{aligned}
l = \sum_{j=1}^m & \{ (N_{j-1} - N_j) \sum_{k=1}^{j-1} \log(p_k q_k) + (a_{2j} + b_{2j}) \log(p_j q_j) \\
& + (d_j + a_{1j}) \log[(1 - p_j) + (1 - \pi_j p_j)(1 - q_j)] \\
& + b_{1j} \log[(1 - q_j) \pi_{j-1}] + a_{2j} \log(1 - \pi_j) + b_{2j} \log \pi_j \} + C, \tag{2}
\end{aligned}$$

where  $N_j$  is the number of live animals at  $t_j$ , and  $C$  is the constant term of a multinomial likelihood function. In the log-likelihood function in (2), the total of  $d_j + a_{1j}$  is known, but the individual information on  $d_j$  and  $a_{1j}$  is not available. The MLE's,  $\hat{\pi}_j$ ,  $\hat{p}_j$ , and  $\hat{q}_j$ , can be obtained by maximizing (2) subject to the constraints

$$0 \leq \pi_j \leq 1, 0 \leq p_j \leq 1, 0 \leq q_j \leq 1 \text{ and } \pi_j p_j \leq \pi_{j-1} \text{ for } j = 1, \dots, m \tag{3}$$

through a numerical method. Ahn et al. (2000) used the Complex Method (Box, 1965) to obtain the MLE's.

Ahn et al. introduced the tumor lethality parameter

$$\begin{aligned}
\lambda_j &= \Pr(\text{tumor causes death} | \text{death with tumor}) \\
&= \frac{(1 - p_j)}{(1 - p_j) + (1 - \pi_j p_j)(1 - q_j)}, \quad j = 1, \dots, m. \tag{4}
\end{aligned}$$

The estimated lethality parameter,  $\hat{\lambda}_j$ , is calculated by substituting the MLE's of  $\pi_j$ ,  $p_j$ , and  $q_j$  into (4). The number of deaths from fatal tumor in the  $j$ th interval is estimated (imputed) to be

$$\hat{d}_j = \hat{\lambda}_j (d_j + a_{1j}),$$

and the imputed number of deaths with incidental tumor in the  $j$ th interval is

$$\hat{a}_{1j} = (1 - \hat{\lambda}_j)(d_j + a_{1j}).$$

From the formulation of (4), we see that if the tumor is always nonlethal,  $\lambda_j = 0$  as expected since  $p_j = 1$ . However, if the tumor is always instantly lethal,  $\lambda_j$  ranges from 0.5 to 1 depending on the

competing risks survival rate (CRSR) since  $\lambda = 1/(2 - q_j)$  is obtained when  $\pi = 1$ . Most types of occult tumors are neither always nonlethal nor always instantly lethal. Instead, usually some tumors are judged to be fatal (the COD) by pathologists and some to be nonfatal (incidental).

As described in Ahn et al. (2000), the standard error estimates of  $\hat{\pi}_j$ ,  $\hat{p}_j$  and  $\hat{q}_j$  can be obtained from the information matrix based on the log-likelihood and the standard error estimate of  $\hat{\lambda}_j$  can be calculated using the delta method applied to (4). The standard error estimate of  $\hat{d}_j$  can be obtained using  $\text{Var}(\hat{d}_j) = (d_j + a_{1j})^2 \text{Var}(\hat{\lambda}_j)$  from (2).

Integer values of  $\hat{d}_j$  and  $\hat{a}_{1j}$  are needed for implementing the test of Peto et al. (1980). These can be obtained by dropping the fractional part (flooring) or rounding up (ceiling) the real values. After combining all dose groups, let the ratio of the number of natural tumor deaths and the total number of natural deaths be a tumor-death ratio, and the ratio of the number of animals having the tumor of interest among sacrificed animals and the total number of sacrificed animals a tumor-sacrifice ratio. The ceiling function is applied to  $\hat{d}_j$  when the tumor-death ratio is higher than a constant factor times the tumor-sacrifice ratio. A high tumor-death ratio compared to the tumor-sacrifice ratio implies a highly lethal tumor. Otherwise, the flooring function is applied to  $\hat{d}_j$ . Since  $d_j$  tends to be underestimated for highly lethal tumors and overestimated for low-lethal tumors (see Ahn et al., 2000), this flooring-ceiling approach helps to reduce the bias of the estimation.

### 3 Newton-Based Optimization Method

We propose a Newton-based method for finding the maximum of a log-likelihood function given in (2) under the constraint of (3).

The problem in Section 2 can be expressed as a nonlinear constrained optimization problem

$$\max_{\pi_j, p_j, q_j} l(\pi_1, \dots, \pi_m, p_1, \dots, p_m, q_1, \dots, q_m) \quad (5)$$

subject to (3). Therefore,  $l : R^{3m} \rightarrow R^1$ . The problem (5) has  $3m$  parameters, the lower and upper bounds for  $3m$  parameters, and nonlinear constraints for  $2(m - 1)$  parameters. Standard optimization routines often fail to give a solution due to the complexity of the problem. The Complex routine by Box (1965) was used to find a maximum in Ahn et al. (2000), but the convergence

of the method was very slow. In this paper, we propose a maximum likelihood estimation using an algorithm based on Newton's method which has a fast convergence for the maximum of (2).

A quadratic convergence rate of Newton's method is possible to obtain with a properly chosen initial guess which resides in the domain of contraction. Newton's method is commonly used for an unconstrained problem. When Newton's method is used for a constrained optimization problem such as (5), modifications are necessary to satisfy the bounds on the parameters and the nonlinear constraints.

The optimization problem  $l : R^{3m} \rightarrow R^1$  of (5) is first converted to a system of nonlinear equations  $F : R^{3m} \rightarrow R^{3m}$ . The likelihood function attains the maximum at the point where the partial derivatives of the function with respect to the parameters  $\pi_j, p_j$  and  $q_j$  are zero.

The partial derivatives with respect to  $p_j, q_j$  and  $\pi_j$  are

$$\frac{\partial l}{\partial p_j} \equiv f_j = \frac{N_j - N_m}{p_j} + \frac{a_{2j} + b_{2j}}{p_j} - \frac{[1 + \pi_j(1 - q_j)](d_j + a_{1j})}{(1 - p_j) + (1 - \pi_j p_j)(1 - q_j)},$$

$$\frac{\partial l}{\partial q_j} \equiv g_j = \frac{N_j - N_m}{q_j} + \frac{a_{2j} + b_{2j}}{q_j} + \frac{(\pi_j p_j - 1)(d_j + a_{1j})}{(1 - p_j) + (1 - \pi_j p_j)(1 - q_j)} - \frac{b_{1j}}{1 - q_j},$$

$$\frac{\partial l}{\partial \pi_j} \equiv h_j = -\frac{p_j(1 - q_j)(d_j + a_{1j})}{(1 - p_j) + (1 - \pi_j p_j)(1 - q_j)} + \frac{b_{1,j+1}}{\pi_j} I[j < m] - \frac{a_{2j}}{1 - \pi_j} + \frac{b_{2j}}{\pi_j},$$

respectively, where  $I(\cdot)$  is the indicator function, and  $b_{1,m+1} = 0$ , where  $j = 1, \dots, m$ . We have a system of  $3m$  nonlinear equations with  $3m$  parameters.

Let  $F = (f_1, \dots, f_m, g_1, \dots, g_m, h_1, \dots, h_m)^T$ . Then the above equations can be rewritten as

$$F(\mathbf{x}) = 0, \tag{6}$$

where  $\mathbf{x} = (p_1, \dots, p_m, q_1, \dots, q_m, \pi_1, \dots, \pi_m)^T$  and  $F : R^{3m} \rightarrow R^{3m}$  with the constraint of (3). The maximum of function  $l$  in (2) occurs at the solution of  $F(\mathbf{x}) = 0$ .

Newton's method can be applied to solve (6) for  $\mathbf{x}$ . A nonlinear system with a large number of equations and parameters such as (6) is difficult to solve with standard numerical methods

(Dennis and Schnabel, 1983). However, the relationship among the parameters and the functions  $f_j = 0$ ,  $g_j = 0$ ,  $h_j = 0$  leads to a smaller size of systems of nonlinear equations.

The equations  $f_j = 0$ ,  $g_j = 0$  and  $h_j = 0$  involve  $p_j$ ,  $q_j$  and  $\pi_j$ . The equations do not have  $p_k$ ,  $q_k$  and  $\pi_k$ , where  $k \neq j$ . Therefore,  $f_j = 0$ ,  $g_j = 0$  and  $h_j = 0$  are solved together for  $p_j$ ,  $q_j$  and  $\pi_j$ . Define

$$G_j(\mathbf{y}) = \begin{pmatrix} f_j(\mathbf{y}) \\ g_j(\mathbf{y}) \\ h_j(\mathbf{y}) \end{pmatrix},$$

where  $\mathbf{y} = (p_j, q_j, \pi_j)^T$ ,  $j = 1, \dots, m$ . The  $m$  systems of 3 nonlinear equations  $G_j(\mathbf{y})$  can be solved separately.

Newton's method is used  $m$  times for a root of the system  $G_j(\mathbf{y})$  of 3 nonlinear equations. Since the order of solving  $G_j(\mathbf{y})$  does not affect the solution of (6), the equations are solved from the  $m$ -th system  $G_m$  to the system  $G_1$ . This enables us to determine the lower bound for  $\pi_{j-1}$  from  $p_j$  and  $\pi_j$  for  $j = 2, \dots, m$ .

Convergence of Newton's method depends on the choice of an initial guess. In (2), the parameters  $p_j$ ,  $q_j$ ,  $\pi_j$  and  $\pi_j p_j$  are in  $[0, 1]$  and so are  $1 - p_j$ ,  $1 - q_j$ ,  $1 - \pi_j$  and  $1 - \pi_j p_j$ . If the values of  $\pi_j$  and  $q_j$  are fixed, then the terms in (2) are a linear combination of  $\log p_j$  and  $\log[1 + \alpha - (1 + \alpha\beta)p_j]$  for each  $j$ , for some  $\alpha$  and  $\beta$  in  $[0, 1]$  such that  $\alpha \geq \alpha\beta$ . Since  $\log p_j$  is strictly increasing and  $\log[1 + \alpha - (1 + \alpha\beta)p_j]$  is strictly decreasing in  $[0, 1]$ , a linear combination of these has one local maximum in  $[0, 1]$ . Similarly, (5) has a local maximum for the parameters  $\pi_j$  and  $q_j$  in  $[0, 1]$ . Hence, if the signs of the partial derivative of the log-likelihood function with respect to one of  $p_j$ ,  $q_j$  and  $\pi_j$  at the end points of  $[0, 1]$  are positive, the log-likelihood function is increasing for the variable and the maximum of the function occurs when the variable is near 1. The negative signs of the partial derivative with respect to a variable at both the ends of  $[0, 1]$  indicate that 0 is close to the MLE in  $[0, 1]$ . An extreme value occurs in the middle of  $[0, 1]$  if the signs of a partial derivative of the function are opposite at the end points of  $[0, 1]$ .

At the beginning of the Newton iteration, the interval  $[0, 1]$  is divided into small subintervals and the function values of (5) are computed with the values of  $p_j$ ,  $q_j$  and  $\pi_j$  at the end points of the subintervals. We then find a subinterval where the signs of the function values of  $f_j$  at the endpoints

are opposite, and the midpoint of the subinterval is given as an initial guess for  $p_j$ . Similarly, the midpoints of the subintervals where the signs of the function values of  $g_j$  and  $h_j$  at the endpoints are opposite are given as initial guesses for  $q_j$  and  $\pi_j$ , respectively. The initial guesses given this way can be very accurate as the number of the subintervals is increased. The Jacobian matrix of  $G(\mathbf{y})$  is obtained from a divided difference formula, i.e., the  $i$ -th column of the Jacobian is

$$J(\cdot, i) = \frac{G(\mathbf{y} + \delta e_i) - G(\mathbf{y})}{\delta},$$

where  $e_i$  is a unit vector in the  $i$ -th component. In this study,  $\delta = 10^{-4}$  is used.

As the Newton iterations are performed, the lower and upper bounds for each variable are examined. If an updated approximation to the root does not satisfy the upper and lower bounds, the upper and lower bounds become approximate solutions at that iteration. Large Newton steps may result in approximate solutions outside the bounds during the iterations. A line search can be used to find the length of the step which minimizes the values of (5) at the bounds. In the present experiments, a very small step in the direction of the Newton step is taken instead of a line search algorithm to reduce computing time. The current approximation to the root is updated with the obtained Newton step only when the updated approximate solution is smaller in 2-norm of  $G$ . The maximum iteration number for Newton's method was set to 8 in this study. The initial guesses are close to the solution and most of the experiments converge in less than 8 Newton iterations. Other Newton method stopping criteria in computational experiments are  $\|G\| > 10^8$ ,  $\|G\| < 10^{-7}$ , and Newton step size  $< 10^{-7}$ . The algorithm of this method including the initial values and parameter settings is given in the Appendix.

## 4 Simulation Study

### 4.1 Design of Monte Carlo Simulation Study

A Monte Carlo simulation study was conducted to compare the performance of the proposed Newton-based optimization method with the Complex method used in Ahn et al. (2000) for the constrained NPMLE method. For the two optimization methods, the accuracy of the attribution of tumor lethality was compared.

In the simulation, a bioassay design with 50 animals in a group was considered. The last two of the NTP intervals (Bailer and Portier, 1988) were combined for utilizing the information concerning the tumor development from sacrificed animals in an extended interval. Thus, the proposed procedure was simulated to have three intervals with time points at 52, 78 and 104 weeks for both the incidental and fatal tumors. All the remaining live animals were sacrificed at the end of the experiment.

It was assumed that three independent random variables completely determined the observed outcome for each animal. The random variables were the time to onset of tumor,  $T_1$ , the time after onset until death from the tumor,  $T_2$ , and the time to death from a competing risk,  $X_C$ . Note that  $T_1 + T_2 = T_D$ , where  $T_D$  represents the overall time to death from the tumor of interest. Thus the tumor of interest was present in an animal at the time of death if  $T_1 \leq \min\{X_C, X_S\}$ , where  $X_S$  denotes the terminal sacrifice time. An animal died from the tumor of interest if  $T_D \leq \min\{X_C, X_S\}$ . Otherwise, it died from a competing risk including sacrifice.

Distributions of time to onset and time to death were of the form used by Portier et al. (1986). The distribution of time to onset of tumor,  $T_1$ , was modeled by the survival function

$$S(t) = \exp \left[ -\theta \delta_1 (t/104)^{\delta_2} \right],$$

where  $\delta_1 \geq 0$ ,  $\delta_2 \geq 0$ ,  $\theta = e^\ell \geq 1$ , and  $\ell$  is the dose level. The value of  $\delta_2$  was set to be 3 for Weibull-distributed data and was set to be 1 for the exponentially distributed data. The parameter  $\theta$  was set to be 1 so that the dose level  $\ell = 0$ , and  $\delta_1 = -\ln[S(104)]$  was chosen such that the probability of tumor onset by 104 weeks,  $1 - S(104)$ , was 0.05, 0.3 or 0.6.

The survival function for time to death from competing risks,  $X_C$ , was taken to be

$$Q(t) = \exp[-\phi(\gamma_1 t + \gamma_2 t^{\gamma_3})],$$

where  $\phi \geq 1$ ,  $\gamma_1 \geq 0$ ,  $\gamma_2 \geq 0$  and  $\gamma_3 \geq 0$ . With  $\phi = 1$ ,  $\gamma_1 = 10^{-4}$  and  $\gamma_2 = 10^{-16}$ ,  $\gamma_3$  was chosen to be 7.42553074 such that the probability of survival with respect to competing risks at 104 weeks became 0.9. The value of  $\phi$  varied such that  $\phi = \ln(\psi)/\ln(0.9)$ , if the survival rate was  $\psi$ . The value of  $\phi$  varied such that the competing risk survival rate (CRSR) became 0.2 and 0.5.

The survival function for time to death from tumor,  $T_2$ , had the same form as that for death from competing risks, and the values of  $\gamma_1$ ,  $\gamma_2$  and  $\gamma_3$  remained the same. The parameter  $\phi$  for data with Weibull-distributed tumor onset was selected to reflect low tumor lethality (approximately 5% of observed tumors are COD), intermediate tumor lethality (approximately 35% of observed tumors are COD), and high tumor lethality (approximately 90% of observed tumors are COD).

Five thousand simulated data sets with both Weibull and exponential tumor onset distributions were generated for each combination of three tumor onset probabilities at 104 weeks, three tumor lethality rates, and two CRSR's. Thus, a total of 18 configurations were considered for each model of the tumor onset distribution.

## 4.2 Simulation Results for Estimation

The estimated number of deaths from fatal tumor ( $d_j$ ) obtained using the Newton-based approach was compared with that obtained using the Complex Method. For each interval in each configuration, the average of  $d_j$  and the average of  $\hat{d}_j$  out of the 5000 data sets were calculated and compared. To calculate the estimation errors, let  $d_{jk}$  denote the number of fatal tumors for the  $j$ th interval in the  $k$ th simulation data set, and let  $\hat{d}_{jk}$  represent the estimate of  $d_{jk}$ . The averages  $\bar{d}_j = \sum_{k=1}^{5000} d_{jk}/5000$  and  $\bar{\hat{d}}_j = \sum_{k=1}^{5000} \hat{d}_{jk}/5000$  were calculated. The bias is defined as  $B_j = \bar{\hat{d}}_j - \bar{d}_j$  for  $j = 1, 2, 3$ . The Average Net Percentage of Bias (%bias) is defined as the rate of overestimation for either the number of fatal tumors or the number of incidental tumors across the intervals. That is,  $\%bias = 100 \times \left( \sum_{j=1}^3 B_j / \sum_{j=1}^3 x_j \right)$ , where  $x_j = \bar{a}_{1j}$  if the average number of fatal tumors is overestimated in the  $j$ th interval, and  $x_j = \bar{d}_j$  if the average number of incidental tumors is overestimated in the  $j$ th interval. A positive value of %bias indicates a tendency to overestimate the number of fatal tumors, and a negative value of %bias indicates a tendency to overestimate the number of incidental tumors.

The simulation results are given in Tables 1 to 4. The average number of deaths from fatal tumor obtained from the two optimization methods turned out to be very close. For Weibull tumor onset data, the number of fatal tumors was underestimated for various tumor rates with highly lethal tumors, and overestimated for low lethal tumors. For exponential tumor onset data, the number of fatal tumors was overestimated for low lethal tumors. It became worse with increasing tumor rate. For moderate and highly lethal tumors, the estimation of tumor lethality was reasonably accurate.

Since data with a single terminal sacrifice provides less information than multiple sacrifice data, estimation is expected to be more accurate for multiple sacrifice data.

## 5 Example: ED<sub>01</sub> Study

An experiment was conducted at the National Center for Toxicological Research to study the effect of feeding 2-acetylaminofluorene (2-AAF) to female BALB/C mice (ED<sub>01</sub> study; Littlefield et al., 1980). Data in Table 5 are from groups of animals that were dosed continuously at concentrations of 0, 35, 75, or 150 ppm 2-AAF until the terminal sacrifice at 726 days. The tumors of interest were hepatocellular adenomas or carcinomas of the liver. The animals were from only one room (room 141) out of 3 rooms that had a 24-month sacrifice. These were only animals that were designated to be sacrificed at 24 months.

Table 6 shows the estimated quantities and standard errors using the two optimization methods. The two methods gave identical estimates of the number (integer) of fatal tumors. Figures 1 through 4 display contour plots of the log-likelihood function (2) for control, 35 ppm, 75 ppm and 150 ppm groups, respectively, at various combinations of the parameter values. From Table 6 and the figures, we find that the maximum of the log-likelihood was attained inside the interval (0, 1) of  $p_3$  and  $\pi_3$  for the 75 ppm and 150 ppm groups and  $q_3$  for all the groups, but it was attained near 1 for the others.

## 6 Discussion

In a nonlinear constrained optimization problem, standard optimization routines often fail to give a solution due to the complexity of the problem. The Complex Method by Box (1965) was used to find the maximum likelihood estimator in Ahn et al. (2000). Since the Complex Method is based on a sequential direct search technique without differentiation, it is slow and difficult to implement. The proposed Newton-based approach improves this optimization procedure in the following ways: First, a quadratic convergence rate of Newton's method substantially reduces the computing time. Second, Newton's method based on partial derivatives of the loglikelihood function can be easily implemented. The proposed method can be applied to other optimization problems in an animal

Table 1: Estimated number of fatal tumors from simulated Weibull-distributed tumor onset data with competing risks survival rate 0.5. For each interval, average was taken from 5000 trials.

Tumor onset prob. <sup>a</sup>	Tumor lethality prob. <sup>b</sup>	$j^c$	Newton Method					Complex Method		
			$d_j + a_{1j}$	$d_j$	$\hat{d}_j$	se( $\hat{d}_j$ )	%bias	$\hat{d}_j$	se( $\hat{d}_j$ )	%bias
0.05	$\simeq 0.05$	1	0.008	0.006	0.001	0.093	12.4	0.002	0.086	12.4
		2	0.081	0.023	0.010	0.220		0.011	0.220	
		3	0.753	0.064	0.171	0.546		0.167	0.548	
	$\simeq 0.35$	1	0.058	0.056	0.023	0.239	-34.3	0.024	0.223	-34.3
		2	0.262	0.217	0.088	0.373		0.089	0.373	
		3	0.906	0.420	0.344	0.608		0.342	0.609	
	$\simeq 0.90$	1	0.253	0.253	0.233	0.495	-5.5	0.233	0.530	-5.6
		2	0.648	0.642	0.597	0.532		0.597	0.533	
		3	1.024	0.946	0.910	0.771		0.907	0.771	
0.30	$\simeq 0.05$	1	0.059	0.038	0.008	0.254	13.7	0.012	0.231	13.7
		2	0.544	0.147	0.131	0.529		0.139	0.530	
		3	4.626	0.374	1.026	1.279		1.014	1.277	
	$\simeq 0.35$	1	0.399	0.382	0.121	0.645	-30.7	0.125	0.641	-30.7
		2	1.631	1.316	0.836	0.741		0.842	0.744	
		3	5.445	2.433	1.907	1.054		1.894	1.054	
	$\simeq 0.90$	1	1.679	1.673	1.645	1.142	-11.0	1.644	1.116	-11.2
		2	4.083	4.013	4.012	0.847		4.012	0.853	
		3	5.827	5.342	4.158	0.756		4.142	0.760	
0.60	$\simeq 0.05$	1	0.163	0.094	0.024	0.486	19.1	0.035	0.452	19.2
		2	1.276	0.350	0.568	0.803		0.589	0.791	
		3	9.671	0.772	2.515	2.004		2.496	2.002	
	$\simeq 0.35$	1	0.901	0.839	0.385	0.947	-13.7	0.392	0.997	-13.8
		2	3.525	2.786	2.572	0.967		2.575	0.960	
		3	11.166	4.727	4.254	1.645		4.232	1.644	
	$\simeq 0.90$	1	4.003	3.981	3.940	1.943	-13.6	3.873	1.870	-14.0
		2	8.912	8.741	8.516	1.131		8.510	1.160	
		3	10.977	9.868	7.065	0.811		7.040	0.810	

<sup>a</sup>Cumulative tumor onset probability at 104 weeks in absence of competing risks.

<sup>b</sup>Proportion of observed tumors that actually result in death.

<sup>c</sup>Time intervals 1-3 represent, respectively, 0-52, 52-78, 78-104 weeks.

Table 2: Estimated number of fatal tumors from simulated Weibull-distributed tumor onset data with competing risks survival rate 0.2. For each interval, average was taken from 5000 trials.

Tumor onset prob. <sup>a</sup>	Tumor lethality prob. <sup>b</sup>	$j^c$	Newton Method					Complex Method		
			$d_j + a_{1j}$	$d_j$	$\hat{d}_j$	se( $\hat{d}_j$ )	%bias	$\hat{d}_j$	se( $\hat{d}_j$ )	%bias
0.05	$\simeq 0.05$	1	0.015	0.007	0.002	0.149	20.3	0.002	0.142	20.3
		2	0.145	0.023	0.021	0.344		0.021	0.344	
		3	0.976	0.042	0.245	0.555		0.245	0.555	
	$\simeq 0.35$	1	0.073	0.066	0.018	0.334	-7.8	0.019	0.336	-7.7
		2	0.287	0.192	0.093	0.468		0.093	0.468	
		3	0.936	0.259	0.333	0.552		0.333	0.552	
	$\simeq 0.90$	1	0.249	0.247	0.227	0.593	-5.2	0.227	0.604	-5.2
		2	0.597	0.581	0.549	0.630		0.549	0.630	
		3	0.717	0.614	0.618	0.527		0.618	0.527	
0.30	$\simeq 0.05$	1	0.088	0.040	0.004	0.393	27.8	0.005	0.422	27.7
		2	0.981	0.143	0.355	0.799		0.355	0.799	
		3	6.095	0.244	1.938	0.935		1.928	0.936	
	$\simeq 0.35$	1	0.414	0.372	0.076	0.794	-0.7	0.077	0.996	-0.8
		2	1.874	1.214	1.014	0.925		1.014	0.925	
		3	5.773	1.584	2.040	0.790		2.034	0.791	
	$\simeq 0.90$	1	1.642	1.629	1.602	1.312	-10.3	1.592	1.554	-10.5
		2	3.764	3.624	3.567	0.983		3.563	0.982	
		3	4.321	3.612	2.784	0.628		2.782	0.630	
0.60	$\simeq 0.05$	1	0.218	0.091	0.024	0.657	36.7	0.026	0.831	36.6
		2	2.243	0.319	1.333	1.095		1.330	1.092	
		3	12.908	0.487	4.841	1.391		4.823	1.395	
	$\simeq 0.35$	1	0.922	0.807	0.316	1.189	15.5	0.314	1.671	15.4
		2	4.063	2.523	2.953	1.147		2.949	1.442	
		3	12.155	3.103	4.926	1.162		4.920	1.162	
	$\simeq 0.90$	1	3.870	3.831	3.779	1.954	-14.5	3.665	2.105	-14.9
		2	8.324	7.965	7.270	1.163		7.258	1.160	
		3	8.247	6.655	4.729	0.614		4.781	0.596	

<sup>a</sup>Cumulative tumor onset probability at 104 weeks in absence of competing risks.

<sup>b</sup>Proportion of observed tumors that actually result in death.

<sup>c</sup>Time intervals 1-3 represent, respectively, 0-52, 52-78, 78-104 weeks.

Table 3: Estimated number of fatal tumors from simulated exponentially distributed tumor onset data with competing risks survival rate 0.5. For each interval, average was taken from 5000 trials.

Tumor onset prob. <sup>a</sup>	Tumor lethality prob. <sup>b</sup>	$j^c$	Newton Method					Complex Method		
			$d_j + a_{1j}$	$d_j$	$\hat{d}_j$	$se(\hat{d}_j)$	%bias	$\hat{d}_j$	$se(\hat{d}_j)$	%bias
0.05	$\simeq 0.05$	1	0.035	0.010	0.006	0.197	18.9	0.011	0.191	19.2
		2	0.149	0.021	0.027	0.288		0.028	0.288	
		3	0.907	0.070	0.255	0.578		0.252	0.579	
	$\simeq 0.35$	1	0.153	0.129	0.070	0.404	-8.5	0.075	0.393	-8.2
		2	0.327	0.221	0.129	0.414		0.130	0.414	
		3	0.989	0.368	0.436	0.623		0.433	0.624	
	$\simeq 0.90$	1	1.057	1.048	1.020	0.894	0.8	1.021	0.857	0.8
		2	0.591	0.574	0.563	0.509		0.563	0.509	
		3	0.534	0.453	0.505	0.622		0.505	0.622	
0.30	$\simeq 0.05$	1	0.232	0.069	0.037	0.486	22.2	0.066	0.477	22.8
		2	0.940	0.116	0.332	0.598		0.348	0.599	
		3	5.492	0.376	1.529	1.290		1.519	1.289	
	$\simeq 0.35$	1	0.901	0.753	0.402	0.865	-6.4	0.425	0.904	-5.9
		2	1.921	1.168	1.075	0.728		1.092	0.732	
		3	6.054	2.265	2.346	1.044		2.333	1.045	
	$\simeq 0.90$	1	6.337	6.283	6.275	2.018	0.2	6.270	1.737	0.0
		2	3.610	3.462	3.583	0.767		3.583	0.782	
		3	3.053	2.461	2.364	0.708		2.356	0.743	
0.60	$\simeq 0.05$	1	0.531	0.126	0.151	0.693	30.8	0.209	0.614	31.7
		2	2.018	0.228	1.159	0.819		1.235	0.784	
		3	11.135	0.779	3.691	1.999		3.666	1.998	
	$\simeq 0.35$	1	1.832	1.446	1.129	1.130	9.7	1.165	0.909	10.1
		2	3.781	2.199	2.856	0.934		2.893	0.884	
		3	12.576	4.702	5.417	1.652		5.388	1.652	
	$\simeq 0.90$	1	13.694	13.532	12.736	3.171	-6.7	12.874	2.528	-6.1
		2	7.229	6.912	7.013	0.984		7.002	1.070	
		3	5.576	4.333	3.816	0.693		3.795	0.700	

<sup>a</sup>Cumulative tumor onset probability at 104 weeks in absence of competing risks.

<sup>b</sup>Proportion of observed tumors that actually result in death.

<sup>c</sup>Time intervals 1-3 represent, respectively, 0-52, 52-78, 78-104 weeks.

Table 4: Estimated number of fatal tumors from simulated exponentially distributed tumor onset data with competing risks survival rate 0.2. For each interval, average was taken from 5000 trials.

Tumor onset prob. <sup>a</sup>	Tumor lethality prob. <sup>b</sup>	$j^c$	Newton Method					Complex Method		
			$d_j + a_{1j}$	$d_j$	$\hat{d}_j$	$se(\hat{d}_j)$	%bias	$\hat{d}_j$	$se(\hat{d}_j)$	%bias
0.05	$\simeq 0.05$	1	0.065	0.011	0.009	0.320	24.3	0.009	0.343	24.3
		2	0.302	0.018	0.066	0.484		0.066	0.484	
		3	1.220	0.044	0.356	0.592		0.356	0.592	
	$\simeq 0.35$	1	0.189	0.137	0.065	0.533	11.5	0.065	0.546	11.5
		2	0.432	0.192	0.181	0.555		0.181	0.555	
		3	1.123	0.234	0.457	0.583		0.457	0.583	
	$\simeq 0.90$	1	1.046	1.031	1.004	1.085	5.8	1.004	1.115	5.8
		2	0.556	0.520	0.531	0.601		0.531	0.601	
		3	0.418	0.306	0.390	0.433		0.390	0.433	
0.30	$\simeq 0.05$	1	0.429	0.061	0.081	0.832	36.3	0.087	1.071	36.2
		2	1.846	0.120	0.988	0.906		0.989	0.906	
		3	7.438	0.257	2.736	0.914		2.723	0.915	
	$\simeq 0.35$	1	1.114	0.753	0.449	1.226	19.6	0.453	1.503	19.5
		2	2.594	1.090	1.652	0.940		1.651	0.939	
		3	6.932	1.461	2.718	0.784		2.709	0.784	
	$\simeq 0.90$	1	6.266	6.139	6.101	2.159	3.3	6.075	2.120	2.8
		2	3.459	3.189	3.326	0.907		3.322	0.906	
		3	2.586	1.723	1.861	0.604		1.860	0.609	
0.60	$\simeq 0.05$	1	0.985	0.124	0.361	1.310	45.5	0.373	1.751	45.4
		2	3.961	0.208	2.935	1.080		2.932	1.068	
		3	15.307	0.486	6.358	1.399		6.339	1.401	
	$\simeq 0.35$	1	2.225	1.403	1.338	1.790	33.5	1.312	2.109	33.3
		2	5.308	1.986	4.172	1.093		4.164	1.082	
		3	14.506	3.067	6.366	1.176		6.360	1.176	
	$\simeq 0.90$	1	13.512	13.178	11.814	4.036	-6.4	11.996	3.222	-5.9
		2	7.020	6.348	6.282	0.992		6.271	0.989	
		3	4.805	2.976	2.969	0.585		2.982	0.590	

<sup>a</sup>Cumulative tumor onset probability at 104 weeks in absence of competing risks.

<sup>b</sup>Proportion of observed tumors that actually result in death.

<sup>c</sup>Time intervals 1-3 represent, respectively, 0-52, 52-78, 78-104 weeks.

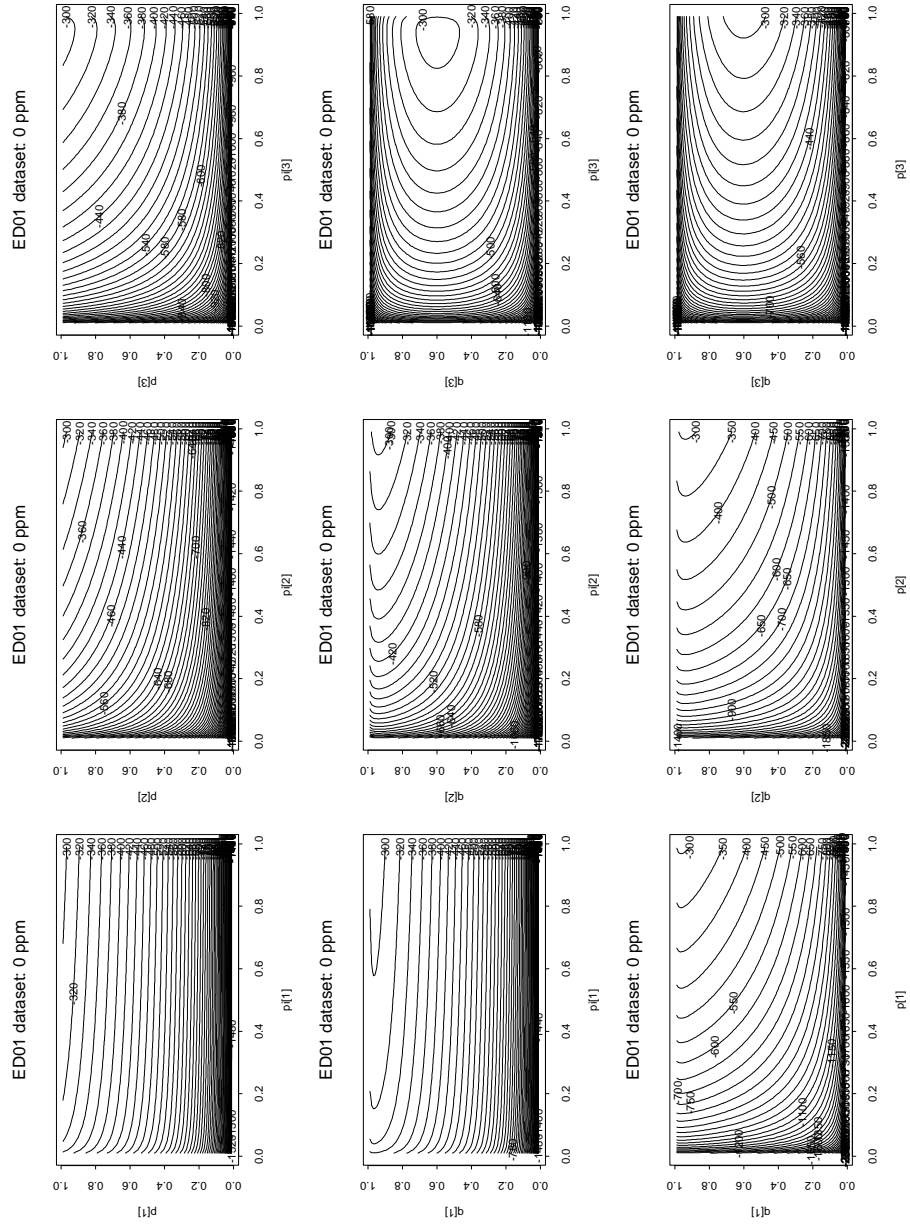


Figure 1: Contour plots of the log-likelihood function (2) for the ED<sub>01</sub> data, control group.

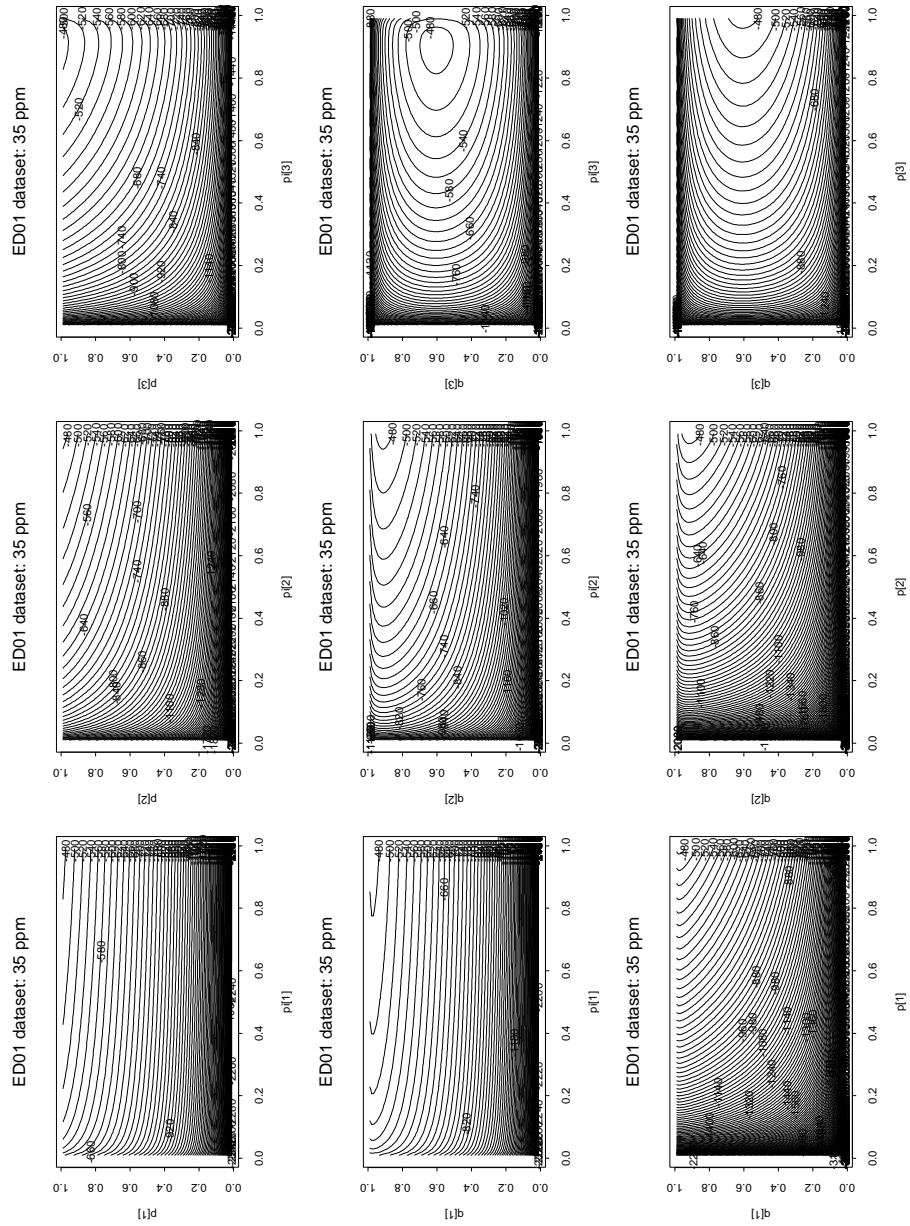


Figure 2: Contour plots of the log-likelihood function (2) for the ED<sub>01</sub> data, 35 ppm group.

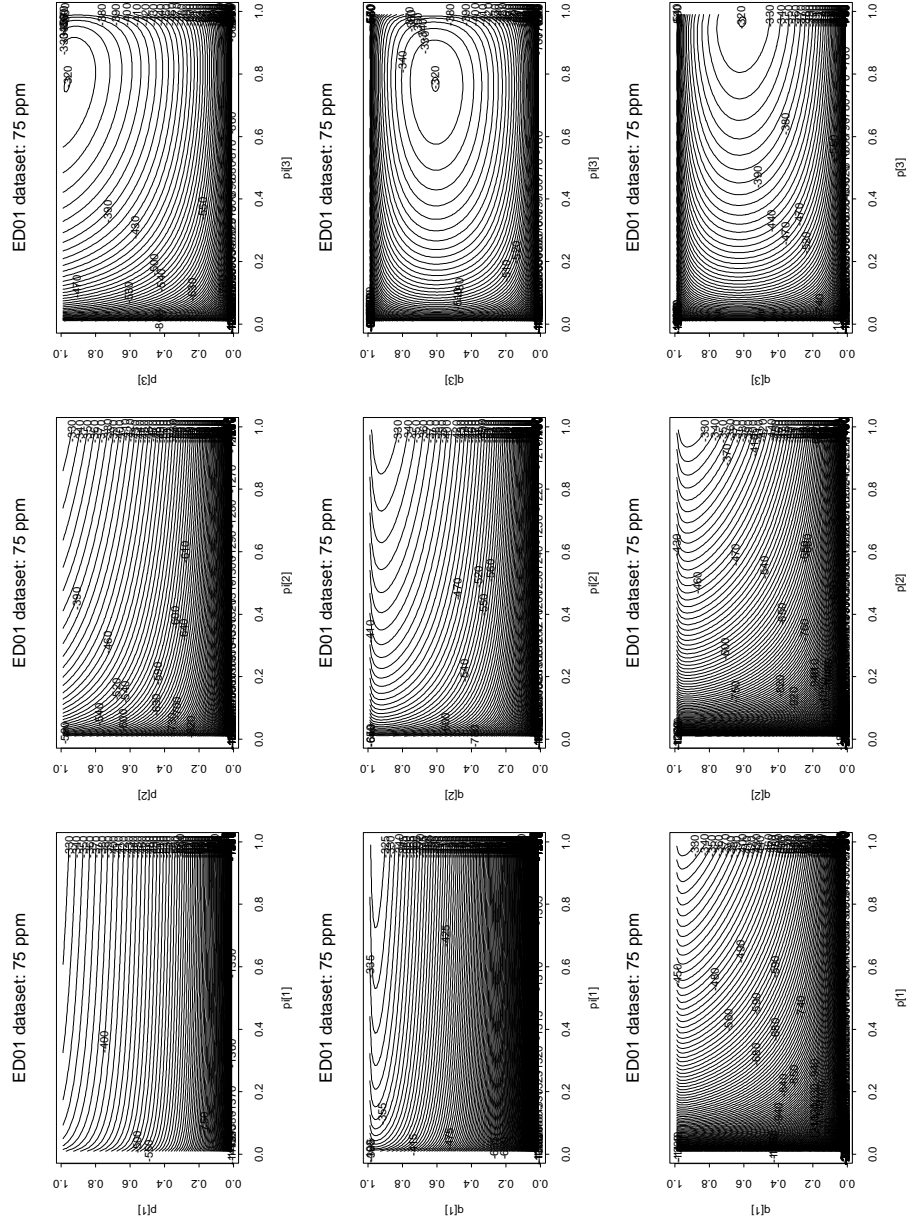


Figure 3: Contour plots of the log-likelihood function (2) for the ED<sub>01</sub> data, 75 ppm group.

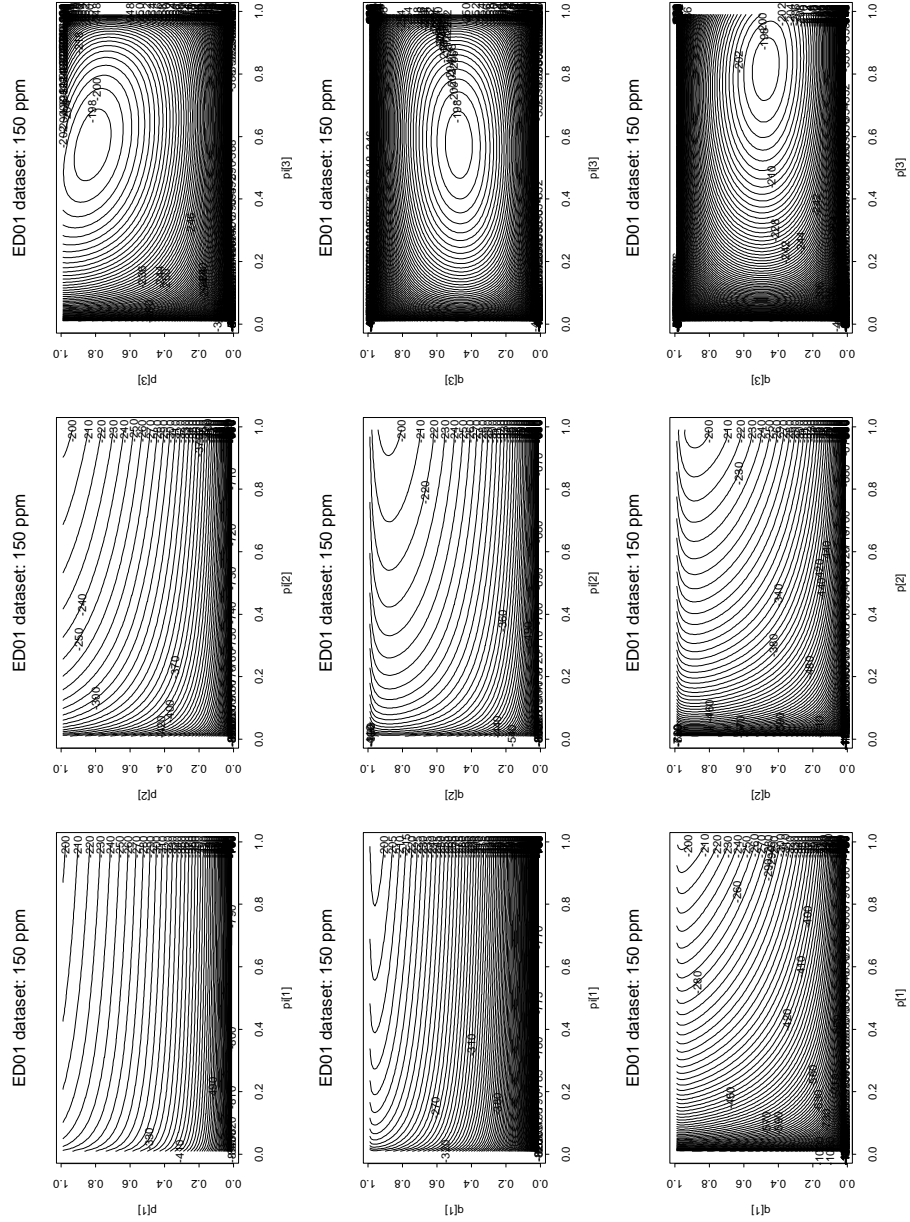


Figure 4: Contour plots of the log-likelihood function (2) for the ED<sub>01</sub> data, 150 ppm group.

Table 5: Frequency data from ED<sub>01</sub> study.

Dose (ppm)	$j^a$	$\tilde{d}_j^b$	$\tilde{d}_j^c$	$ad_j^d$	$b_{1j}$	$a_{2j}$	$b_{2j}$
0	1	0	0	0	9	0	0
	2	0	0	0	15	0	0
	3	0	2	2	94	7	137
35	1	0	0	1	9	0	0
	2	2	3	3	31	0	0
	3	0	1	2	135	18	192
75	1	0	0	0	10	0	0
	2	0	0	1	16	0	0
	3	3	5	13	69	22	101
150	1	0	0	0	5	0	0
	2	1	1	2	14	0	0
	3	8	9	21	42	16	33

<sup>a</sup>Time intervals 1-3 represent, respectively, 0-364, 365-546, 547-726 days.

<sup>b</sup>Imputed number of fatal tumors.

<sup>c</sup>Number of fatal tumors assigned by pathologists.

<sup>d</sup> $d_j + a_{1j}$

carcinogenicity study or in other statistical areas.

According to our simulation study, the estimation of COD by the NPMLE Method using the proposed Newton-based method is as good as that using the Complex Method in terms of bias. As a conclusion, the Newton-based optimization approach is preferable to the Complex Method in the attribution of tumor lethality for occult tumors in the absence of COD information because of simplicity and a substantially short computing time without sacrificing the accuracy.

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Table 6: Estimated quantities for the ED<sub>01</sub> data in Table 5. The values in the parentheses are standard error estimates.

Dose <sup>a</sup>	$j^b$	Newton-based Method				Complex Method				$\hat{d}_j^c$	$d_j^d$	$ad_j^e$
		$\hat{\pi}_j$	$\hat{p}_j$	$\hat{q}_j$	$\hat{\lambda}_j$	$\hat{\pi}_j$	$\hat{p}_j$	$\hat{q}_j$	$\hat{\lambda}_j$			
0	1	1.000 (0.26)	1.000 (0.06)	0.966 (0.01)	* <sup>f</sup>	1.000 (0.26)	1.000 (0.06)	0.966 (0.01)	*	0	0	0
	2	1.000 (0.10)	1.000 (0.06)	0.942 (0.01)	*	1.000 (0.10)	1.000 (0.06)	0.941 (0.01)	*	0	0	0
	3	0.943 (0.02)	1.000 (0.01)	0.601 (0.03)	0.004	0.938 (0.02)	1.000 (0.01)	0.600 (0.03)	0.0	0	2	2
35	1	1.000 (0.21)	0.997 (0.01)	0.977 (0.01)	0.977	1.000 (0.18)	0.997 (0.05)	0.977 (0.008)	0.977	0	0	1
	2	1.000 (0.09)	0.991 (0.01)	0.917 (0.02)	0.923	1.000 (0.09)	0.991 (0.05)	0.917 (0.01)	0.924	2	3	3
	3	0.907 (0.02)	1.000 (0.02)	0.606 (0.03)	0.003	0.906 (0.02)	1.000 (0.02)	0.605 (0.03)	0.0	0	1	2
75	1	1.000 (0.25)	1.000 (0.07)	0.957 (0.01)	*	1.000 (0.25)	1.000 (0.07)	0.957 (0.01)	*	0	0	0
	2	1.000 (0.13)	0.995 (0.01)	0.927 (0.02)	0.931	1.000 (0.12)	0.995 (0.07)	0.927 (0.02)	0.932	0	0	1
	3	0.768 (0.04)	0.968 (0.03)	0.609 (0.04)	0.244	0.767 (0.04)	0.968 (0.03)	0.609 (0.04)	0.244	3	5	13
150	1	1.000 (0.27)	1.000 (0.09)	0.963 (0.02)	*	1.000 (0.27)	1.000 (0.09)	0.962 (0.02)	*	0	0	0
	2	1.000 (0.17)	0.983 (0.02)	0.888 (0.03)	0.898	1.000 (0.15)	0.982 (0.09)	0.887 (0.03)	0.899	1	1	2
	3	0.575 (0.07)	0.821 (0.07)	0.472 (0.05)	0.391	0.574 (0.07)	0.821 (0.07)	0.472 (0.05)	0.391	8	9	21

<sup>a</sup>Dose in ppm.

<sup>b</sup>Time intervals 1-3 represent, respectively, 0-364, 365-546, 547-726 days.

<sup>c</sup>Estimated number of fatal tumors using the proposed method.

<sup>d</sup>Number of fatal tumors assigned by pathologists.

<sup>e</sup> $d_j + a_{1j}$ .

<sup>f</sup>Not available.

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## Appendix: Algorithm for Newton-Based Method

### Parameters:

IterMax=8: maximum number of Newton iterations,  
 tol1 =  $1.e - 8$ , tol2 =  $1.e - 8$ , tol3 =  $1.e + 9$ : stopping criteria in Newton iteration,  
 uBound=0.9999: upper bound for  $p_j$ ,  $q_j$ , and  $\pi_j$ ,  
 lBound=0.0001: lower bound for  $p_j$ ,  $q_j$ , and  $\pi_j$ ,  
 SubintervalSize=1000: size of subintervals of  $[0, 1]$ ,  
 initialPoint= 0.0001, endPoint= 0.9999

### Main iterations for Newton-based Algorithm:

for  $j = m, -1, 1$

**Initialization:**  $i = \text{initialPoint}$ .

**while**  $i \leq \text{endPoint}$ .

    Compute  $f_j(\mathbf{y})$ ,  $g_j(\mathbf{y})$  and  $h_j(\mathbf{y})$  at  $i$ .

$i = i + \text{SubintervalSize}$ .

**endwhile**

for each function  $f_j(\mathbf{y})$ ,  $g_j(\mathbf{y})$  and  $h_j(\mathbf{y})$ ,

**if** ( function value at endPoint  $\geq 0$  and at initialPoint  $\geq 0$  )

        initialGuess = endPoint

**elseif** ( function value at endPoint  $\leq 0$  and at initialPoint  $\leq 0$  )

        initialGuess = initialPoint.

```

elseif ( function values at endPoint and at initialPoint have opposite signs )
    Find a subinterval of (0, 1) at whose end points the function changes signs.
    initialGuess = 2/(endPoint - startPoint of the subinterval).

```

```

endif

```

```

endfor

```

### Newton Iteration:

Set upper and lower bounds for  $p_j$ ,  $q_j$  and  $\pi_{j-1}$ .

iterCounter=1; statusNewton=continue.

**while** (statusNewton == continue)

if( $\|G\| \leq \text{tol1}$ ) statusNewton=end.

Compute newton direction  $d\mathbf{y}$  by solving

$$JG(\mathbf{y}) d\mathbf{y} = -G(\mathbf{y}).$$

if ( $\|G(\mathbf{y}_{\text{new}})\| < \|G(\mathbf{y}_{\text{current}})\|$ )

$$\mathbf{y}_{\text{new}} = \begin{cases} \mathbf{y}_{\text{current}} + d\mathbf{y} & \text{if } l\text{Bound} < \mathbf{y}_{\text{new}} < u\text{Bound} \\ \min\{\mathbf{y}_{\text{current}} + d\mathbf{y}/1000, u\text{Bound}\} & \text{if } \mathbf{y}_{\text{new}} > \text{endPoint} \\ \max\{\mathbf{y}_{\text{current}} + d\mathbf{y}/1000, l\text{Bound}\} & \text{if } \mathbf{y}_{\text{new}} < \text{initialPoint} \end{cases} .$$

**endif**

iterCounter = iterCounter + 1.

dist =  $\|(\mathbf{y})\|$ .

if dist < tol2, statusNewton=end,

elseif dist > tol3, statusNewton = end,

elseif iterCounter > IterMax, statusNewton = end.

**endif**

**endwhile**

**endfor** (End of Main Iteration for  $j$ )