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A New Statistical Formula for Estimating the Breast Cancer's Median Lethal Dose based on Inverse Weibull Model

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Abstract

This paper estimates the median lethal dose of a two-replicate multivariate biological experiment through a new statistical formula related to the best model among eleven models constructed to describe the relationship of dose-response and time based on the inverse Weibull. The real biological experiment focused on using actual data to biologically cure breast cancer using therapeutic zinc selenide, produced either by a plasma-physically approach or by employing an environmental plant extract (Calgan plant). The unknown parameters associated with the eleven models are estimated using two traditional estimation methods: ordinary least squares and maximum likelihood. Because these estimates could not be determined directly, the Newton-Raphson iterative technique is used. The mean squared error is used to choose the best model. Then, at successive time points, the breast cancer's median lethal dose is calculated. The results clearly show that the mean square error values of maximum likelihood are always lower than those of the ordinary least squares, and the median lethal dose exhibits a decreasing relationship over time. Further, the new procedure for measuring the median lethal dose allows for several estimates with subsequent periods, which allows for several effective concentrations of 50% in the experimental units.

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Introduction

The evaluation of the nature or potency of a material (or of a process) using the reaction that results from its application to living matter is known as a biological experiment. In biology, there are two different types of experiments: the univariate quantal response, which is based on the relationship between dose and response, and the multivariate quantal response, which is based on

the relationship between dose-response with time. Evaluation of concentration and predicted doses of radiation resulting from many sources, such as X-ray [1] or uranium concentrations in drinking water [2], is a required aspect for optimizing and minimizing needless radiation doses. On the other side, estimating effective dosages, particularly the median lethal dose (LD_{50}) that kills 50% of experiment objects, is one of the most crucial applications of multivariate quantal experiments. Among many studies processed biological experiments, Gaynntdinov et al. [3] developed an optimal model of radiation–pasteurellosis lesions of the organism since the risk of both isolated and combined lesions of agricultural animals and humans with ionizing radiation and biological agents remains, and they calculated the LD_{50} with different doses. Firman et al. [4] employed Bayesian methodology to construct models relating to the probability that a given substance might belong to one of five categories, each corresponding to a specific LD_{50} range. Alrawe and Alzubaidy [5] used chicks as a biological model to investigate the efficacy of Lambda-Cyhalothrin and estimate LD_{50} over 24 hours at three different doses. As a result, they advised against employing this toxin and limiting its use to houses and farms. Recently, Al-Noor et al. [6] and Jasim et al. [7] employed the modified Weibull model with the maximum likelihood estimation method to estimate the LD_{50} of different real experiments.

The aim of the present paper is to employ the statistical inverse Weibull model with the ordinary least squares and maximum likelihood estimation methods to estimate the LD_{50} of breast cancer data based on a new formula related to the best model among different constructed models.

Inverse Weibull model

The inverse Weibull (IW) model occupies an essential place in representing the lifetime of components and investigating different extreme circumstances retaining rainfall, sea waves, wind speeds, earthquakes, flood queues in supermarkets, etc. [8]. The IW has been used also to model different real-life applications for example degradation of mechanical components such as pistons, crankshafts of diesel engines, and the breakdown of insulating fluid. Further, the IW model has many important applications in reliability engineering, infant mortality, useful life, wear-out periods, life testing, and service records [9] and it can be used to determine the cost-effectiveness and maintenance periods of reliability-centered maintenance activities [10]. Other applications of IW and its generalization can be found in [11-14].

The probability density function (PDF) and cumulative function (CF) of the IW model, with scale parameter (α) and shape parameter (λ), are given respectively by:

$$f(t;\lambda,\alpha) = \alpha\lambda\, t^{-(\lambda+1)} e^{-\alpha t^{-\lambda}};\ t \geq 0, \lambda, \alpha > 0 \quad (1)$$

$$F(t;\lambda,\alpha) = e^{-\alpha t^{-\lambda}} \quad (2)$$

For a biological experiment, suppose there is a linear relationship between the natural–logarithms of the scale parameter and dose, i.e. $\ln(\alpha) = \beta + \gamma\ \ln(d)$. So, the scale parameter is equivalent to

$$\alpha = e^{\beta+\gamma \ln(d)}\ ; -\infty < \beta < \infty\ , \gamma \neq 0 \quad (3)$$

After substituting Eq. (3) in Eq. (1) and Eq. (2), the PDF and CF of a random sample of response times $t_j(t_1, \dots, t_n)$ taken from IW with doses $d_i(d_1, \dots, d_k)$ are given by:

$$f(t_j;\lambda,\beta,\gamma) = e^{\beta+\gamma \ln(d_i)} \lambda t_j^{-(\lambda+1)} e^{-e^{\beta+\gamma\ \ln(d_i)} t_j^{-\lambda}};\ t \geq 0, \lambda > 0, -\infty < \beta < \infty, \gamma \neq 0 \quad (4)$$

$$F(t_j;\lambda,\beta,\gamma) = e^{-t_j^{-\lambda}\, e^{\beta+\gamma \ln(d_i)}} \quad (5)$$

Estimation methods

I. Ordinary Least Squares Estimation Method

In statistics, the ordinary least squares (OLS) or linear least squares is a method for estimating the unknown parameters in a linear regression model. This method minimizes the sum of squared vertical distances between the observed responses in the dataset and the responses predicted by the linear approximation. The OLS procedure minimizes the sum of squared

residuals. It is used in economics (econometrics) and electrical engineering (control theory and signal processing), among many areas of application [15].

Let $t_1, \dots, t_n$ be a random sample from IW model with doses $d_i(d_1, \dots, d_k)$, then the OLS procedure minimizes $\sum_{j=1}^{n} \epsilon_j^2 = \sum_{j=1}^{n} \left(\hat{F}\left(t_j\right) - F(t_j)\right)^2$, with estimated CF $\hat{F}\left(t_j\right) = F\left(t_j, \hat{\lambda}, \hat{\beta}, \hat{\gamma}\right) = e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}$ and empirical CF $F\left(t_j\right) = F_j = \frac{j-0.5}{n}, j = 1, \dots, n$. Now

$$\sum_{j=1}^{n} \epsilon_j^2 = \sum_{j=1}^{n} \left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} - F_j\right)^2 \tag{6}$$

Drive Eq. (6) for the parameters (λ, β, γ) respectively to get

$$\frac{\partial \sum_{j=1}^{n} \epsilon_j^2}{\partial \lambda} = 2 \sum_{j=1}^{n} t_j^{-\lambda} ln\left(t_j\right) e^{\beta+\gamma\ln(d_i) - t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} \left(e^{-t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} - F_j\right)$$

$$\frac{\partial \sum_{j=1}^{n} \epsilon_j^2}{\partial \beta} = -2 \sum_{j=1}^{n} t_j^{-\lambda}\ e^{\beta+\gamma\ln(d_i) - t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} \left(e^{-t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} - F_j\right)$$

$$\frac{\partial \sum_{j=1}^{n} \epsilon_j^2}{\partial \gamma} = -2\ln(d_i) \sum_{j=1}^{n} t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i) - t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} \left(e^{-t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}} - F_j\right)$$

Let $z_1(\lambda)$, $z_2(\beta)$ and $z_3(\gamma)$ represent the partial derivatives of $\sum_{j=1}^{n} \epsilon_j^2$ to λ, β, γ and set it equal to zero, as follows

$$z_1(\lambda) = 2 \sum_{j=1}^{n} t_j^{-\hat{\lambda}} \ln\left(t_j\right) e^{\hat{\beta}+\hat{\gamma}\ln(d_i) - t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} \left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} - F_j\right) = 0 \tag{7}$$

$$z_2(\beta) = -2 \sum_{j=1}^{n} t_j^{-\hat{\lambda}}\ e^{\hat{\beta}+\hat{\gamma}\ln(d_i) - t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\, ln(d_i)}} \left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} - F_j\right) = 0 \tag{8}$$

$$z_3(\gamma) = -2\ln(d_i) \sum_{j=1}^{n} t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i) - t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} \left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} - F_j\right) = 0 \tag{9}$$

Noticing that the Eq. (7) to Eq. (9) are non–linear and difficult to solve in traditional methods. By iterative processes, the three $(\hat{\lambda}, \hat{\beta}, \hat{\gamma})$ OLS estimates can be obtained respectively. With the iterative Newton-Raphson method, the Jacobin matrix is used with iteration (s), as shown below

$$\begin{bmatrix} \lambda_{s+1} \\ \beta_{s+1} \\ \gamma_{s+1} \end{bmatrix} = \begin{bmatrix} \lambda_s \\ \beta_s \\ \gamma_s \end{bmatrix} - J_s^{-1} \begin{bmatrix} z_1(\lambda) \\ z_2(\beta) \\ z_3(\gamma) \end{bmatrix} \tag{10}$$

The OLS estimated values can be obtained iteratively from Eq. (10) until convergence occurs, that is, the absolute value for the difference between two successive iterations $(s, s+1)$ is less than the assumed small error tolerance, $\varepsilon > 0$. When convergence occurs, the current estimates represent the estimates of parameters. We need to mention that with $s = 0$, the $\lambda_0, \beta_0, \gamma_0$ represent the initial values, and the Jacobin matrix must be a non-singular symmetric matrix J_s to obtain its inverse, where

$J_s = \begin{bmatrix} \frac{\partial z_1(\lambda)}{\partial \lambda} & \frac{\partial z_1(\lambda)}{\partial \beta} & \frac{\partial z_1(\lambda)}{\partial \gamma} \\ \frac{\partial z_2(\beta)}{\partial \lambda} & \frac{\partial z_2(\beta)}{\partial \beta} & \frac{\partial z_2(\beta)}{\partial \gamma} \\ \frac{\partial z_3(\gamma)}{\partial \lambda} & \frac{\partial z_3(\gamma)}{\partial \beta} & \frac{\partial z_3(\gamma)}{\partial \gamma} \end{bmatrix}$, and the partial derivatives of Eq. (7) to Eq. (9) concerning to unknown parameters are

$$\frac{\partial z_1(\lambda)}{\partial \lambda} = 2\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\ln(t_j)\right)^2 e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$+2\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\ln(t_j)\right)^2 e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)\right)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)$$

$$-2\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\left(\ln(t_j)\right)^2 e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)$$

$$\frac{\partial z_1(\lambda)}{\partial \beta} = \frac{\partial z_2(\beta)}{\partial \lambda} = -2\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\right)^2\ln(t_j)\,e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$+2\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\ln(t_j)\,e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)\left(1-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)$$

$$\frac{\partial z_1(\lambda)}{\partial \gamma} = \frac{\partial z_3(\gamma)}{\partial \lambda} = -2\ln(d_i)\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\right)^2\ln(t_j)\,e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$+2\ln(d_i)\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\ln(t_j)\,e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)\left(1-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)$$

$$\frac{\partial z_2(\beta)}{\partial \beta} = 2\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\right)^2 e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$-2\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\,e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)\left(1-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)$$

$$\frac{\partial z_2(\beta)}{\partial \gamma} = \frac{\partial z_3(\gamma)}{\partial \beta} = 2\ln(d_i)\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\right)^2 e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$-2\ln(d_i)\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\,e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)\left(1-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)$$

$$\frac{\partial z_3(\gamma)}{\partial \gamma} = 2(\ln(d_i))^2\sum_{j=1}^{n}\left(t_j^{-\hat{\lambda}}\right)^2 e^{2\left(\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)}$$

$$-2(\ln(d_i))^2\sum_{j=1}^{n}t_j^{-\hat{\lambda}}\,e^{\hat{\beta}+\hat{\gamma}\ln(d_i)-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\left(e^{-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}-F_j\right)\left(1-t_j^{-\hat{\lambda}}e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}\right)$$

II. Maximum Likelihood Estimation Method

The good properties, such as consistency, asymptotic unbiased, asymptotic efficiency, and asymptotic normality, make the maximum likelihood estimation the most popular and attractive one. This method gives an optimal estimator for most problems [16].

Let $t_1, \ldots, t_n$ be a random sample from IW model with doses $d_i(d_1, \ldots, d_k)$, then the likelihood function is given by

$$L = \prod_{j=1}^{n}\left(e^{\beta+\gamma\ln(d_i)}\lambda\, {t_j}^{-(\lambda+1)}e^{-e^{\beta+\gamma\ln(d_i)}\,{t_j}^{-\lambda}}\right) \tag{11}$$

Take the natural–logarithm of the likelihood function

$$\ln \mathrm{L} = n\beta + n\gamma \ln(d_i) + n\ln(\lambda) - (\lambda+1)\sum_{j=1}^{n} \ln(t_j) - e^{\beta+\gamma \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\lambda} \quad (12)$$

Drive Eq. (12) for the parameters (λ, β, γ) respectively to get

$$\frac{\partial \ln \mathrm{L}}{\partial \lambda} = \frac{n}{\lambda} - \sum_{j=1}^{n} \ln(t_j) + e^{\beta+\gamma \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\lambda} \ln(t_j)$$

$$\frac{\partial \ln \mathrm{L}}{\partial \beta} = n - e^{\beta+\gamma \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\lambda}$$

$$\frac{\partial \ln \mathrm{L}}{\partial \gamma} = n\ln(d_i) - \ln(d_i)\ e^{\beta+\gamma \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\lambda}$$

Let $g_1(\lambda)$, $g_2(\beta)$ and $g_3(\gamma)$ represent the partial derivatives of $\ln \mathrm{L}$ to λ, β, γ and set it equal to zero, as follows

$$g_1(\lambda) = \frac{n}{\hat{\lambda}} - \sum_{j=1}^{n} \ln(t_j) + e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} \ln(t_j) = 0 \quad (13)$$

$$g_2(\beta) = n - e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} = 0 \quad (14)$$

$$g_3(\gamma) = n\ln(d_i) - \ln(d_i)\ e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} = 0 \quad (15)$$

The ML estimated values of three parameters can be obtained by solving the nonlinear Eq. (13) to Eq. (15) numerically through the iterative Newton-Raphson method as in Eq. (16) until convergence occurs,

$$\begin{bmatrix} \lambda_{s+1} \\ \beta_{s+1} \\ \gamma_{s+1} \end{bmatrix} = \begin{bmatrix} \lambda_s \\ \beta_s \\ \gamma_s \end{bmatrix} - J_s^{-1} \begin{bmatrix} g_1(\lambda) \\ g_2(\beta) \\ g_3(\gamma) \end{bmatrix} \quad (16)$$

where $J_s = \begin{bmatrix} \frac{\partial g_1(\lambda)}{\partial \lambda} & \frac{\partial g_1(\lambda)}{\partial \beta} & \frac{\partial g_1(\lambda)}{\partial \gamma} \\ \frac{\partial g_2(\beta)}{\partial \lambda} & \frac{\partial g_2(\beta)}{\partial \beta} & \frac{\partial g_2(\beta)}{\partial \gamma} \\ \frac{\partial g_3(\gamma)}{\partial \lambda} & \frac{\partial g_3(\gamma)}{\partial \beta} & \frac{\partial g_3(\gamma)}{\partial \gamma} \end{bmatrix}$, and the partial derivatives for unknown parameters are

$$\frac{\partial g_1(\lambda)}{\partial \lambda} = \frac{-n}{\hat{\lambda}^2} - e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} \left(\ln(t_j)\right)^2$$

$$\frac{\partial g_1(\lambda)}{\partial \beta} = \frac{\partial g_2(\beta)}{\partial \lambda} = e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} \ln(t_j)$$

$$\frac{\partial g_1(\lambda)}{\partial \gamma} = \frac{\partial g_3(\gamma)}{\partial \lambda} = \ln(d_i)\, e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}} \ln(t_j)$$

$$\frac{\partial g_2(\beta)}{\partial \beta} = - e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}}$$

$$\frac{\partial g_2(\beta)}{\partial \gamma} = \frac{\partial g_3(\gamma)}{\partial \beta} = -\ \ln(d_i)\, e^{\hat{\beta}+\hat{\gamma} \ln(d_i)} \sum_{j=1}^{n} {t_j}^{-\hat{\lambda}}$$

$$\frac{\partial g_3(\gamma)}{\partial \gamma} = -(\ln(d_i))^2\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)} \sum_{j=1}^{n} t_j^{-\hat{\lambda}}.$$

The initial values of model parameters

It is necessary to indicate the possibility of calculating the initial values of IW parameters $(\lambda_0, \beta_0, \gamma_0)$ by using the CF as follows:

Consider the response time t_j and dose d_i $(j = 1, \dots, n\,; i = 1, \dots, k\,; j = i)$, then the CF in Eq. (5) will be $F(t_j) = F(t_j; \lambda, \beta, \gamma) = e^{-t_j^{-\lambda}\, e^{\beta+\gamma\ln(d_i)}}$, and $F(t_j)$ can be attained through the mean rank formula of empirical CF. After taking the double natural logarithm of two sides and comparing the result with the linear regression model $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$, then $Y = \ln\left(-\ln\left(F(t_j)\right)\right)$, $X_1 = \ln(t_j)\,, X_2 = \ln(d_i)$ with coefficients $\beta_0 = \beta,\ \beta_1 = -\lambda$, and $\beta_2 = \gamma$. Thus, the initial values $(\lambda_0, \beta_0, \gamma_0)$ can be attained easily now by using the OLS method.

The cumulative function

Repeating the biological experiment is vital to confirm that an observed result represents a natural occurrence, and the reproducibility of research has recently gained a lot of attention. One crucial consideration is whether the replicates for each experiment are biological or technical. Technical replicates are repeated measurements of a sample that reveal variations in the measuring equipment and techniques, while biological replicates are biologically separate samples that indicate natural biological variation [17].

Consider C_{ijl} as the cumulative affected numbers that represent the influence of dose i in response time j and replicate l. After getting the parameter's estimates, the C_{ijl} estimate can be obtained based on the CF in Eq. (5) by the following formula:

$$\hat{C}_{ijl} = n_{il}\, \hat{F}(t_j) = n_{il}\, e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}} \qquad (17)$$

where n_{il} represents the number of experimental sample units of dose i and replicate l.

Since the IW contains three parameters, the models' CF may be estimated with and without replication using different models shown in Table 1. The additional last three models are used to investigate the effectiveness of the experiment without replication at specific values of the parameters. The estimated affected numbers (units) can be calculated directly using the cumulative affected numbers obtained from the models' CF estimator in Table 1.

Table 1: Models' cumulative function estimator.

Model	Cumulative function estimator
1	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}_l}\, e^{\hat{\beta}_l+\hat{\gamma}_l\ln(d_i)}}\right)$
2	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}_l+\hat{\gamma}_l\ln(d_i)}}\right)$
3	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}_l}\, e^{\hat{\beta}+\hat{\gamma}_l\ln(d_i)}}\right)$
4	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}_l}\, e^{\hat{\beta}_l+\hat{\gamma}\ln(d_i)}}\right)$
5	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}_l}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\right)$
6	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}_l+\hat{\gamma}\ln(d_i)}}\right)$
7	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}_l\ln(d_i)}}\right)$
8	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\right)$

9	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-1}\, e^{\hat{\beta}+\hat{\gamma}\ln(d_i)}}\right);\lambda = 1$
10	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-\hat{\lambda}}\, e^{1+\hat{\gamma}\ln(d_i)}}\right);\ \beta = 1$
11	$\hat{C}_{ijl} = n_{il}\left(e^{-t_j^{-1}\, e^{1+\hat{\gamma}\ln(d_i)}}\right);\lambda = 1;\beta\ = 1$

Best Fit Model and Median Lethal Dose Estimator

Based on the actual number of affected (observed) units (u_{ijl}), estimated affected units $(\hat{u}_{ijl})$, total number of units (N), and number of model's parameters (p), the best fit model can be chosen with the lowest value of the mean square error (MSE) criterion, where

$$MSE(\hat{u}) = \frac{1}{N-p}\sum_{i,j,l}\left(u_{ijl} - \hat{u}_{ijl}\right)^2;\ i = 1,\dots,k;\ j = 1,\dots,n;\ l = 1,\dots,r \qquad (18)$$

Then, the LD_{50} for the best model can be estimated by making the CF with considered estimated values equal to 0.50, i.e. $\hat{F}(t_j) = e^{-t_j^{-\hat{\lambda}}\, e^{\hat{\beta}+\hat{\gamma}\, ln(d)}} = 0.50$. After taking the double logarithm for two-sided, $\hat{\beta} + \hat{\gamma}\ln(d) - \hat{\lambda}\ln(t_j) = \ln(-\ln(0.50))$, then with $x_j = \ln(d)$, the LD_{50} is equal to

$$LD_{50} = d = e^{x_j};\ x_j = \frac{\hat{\lambda}\ln(t_j) - \hat{\beta} - 0.366513}{\hat{\gamma}} \qquad (19)$$

Real application and results

This section is focused on using biologically accurate data to treat breast cancer, one of the most important threats to public health, with the use of the therapeutic zinc selenide (ZnSe), which was produced in two different ways: first, physically (physical experiment) using plasma and second, environmentally (green experiment) using plant extract (Kalgan plant) (for more details about the experiment, see [18]). Tables 2 and 3 represent the results for the two ways of applying ZnSe on cells for exposure times 24 and 72 hours with four concentrations of ZnSe (mg/ml) ranging between (12.5-100) percent.

Table 2: Response rates of breast cancer cells treated by physically.

Replicate	Time (days)	Dose/Concentration			
		12.5	25	75	100
24 hours	1	0.3774	0.6604	0.7547	0.9057
	2	0.3208	0.5660	0.7925	0.9811
	3	0.1887	0.5472	0.8113	0.9434
	4	0.3019	0.5819	0.7925	0.9434
72 hours	1	0.5077	0.6923	0.8923	0.9692
	2	0.4615	0.7077	0.8769	0.9538
	3	0.4769	0.6923	0.8769	0.9846
	4	0.4769	0.6923	0.8769	0.9692

Table 3: Response rates of breast cancer cells treated by environmentally.

Replicate	Time (days)	Dose/Concentration			
		12.5	25	75	100
24 hours	1	0.4737	0.7895	0.8772	0.9298
	2	0.5088	0.8772	0.9123	0.9825
	3	0.4912	0.7368	0.8421	0.9649
	4	0.4912	0.8070	0.8772	0.9649
72 hours	1	0.6528	0.8194	0.9444	0.9861
	2	0.6250	0.8611	0.9167	0.9583
	3	0.6667	0.8889	0.9306	0.9722
	4	0.6528	0.8611	0.9306	0.9722

The OLS and ML estimates of unknown parameters for each replicate and the entire experiment are obtained by using the program written by MATLAB with initial values $\lambda_0 = 0.712$,

$\beta_0 = 1.601, \gamma_0 = -0.404$ and $\varepsilon = 0.001$. The results are given in Tables 4 and 5. Further, the OLS and ML estimated values corresponding to each model are given in Tables 6 and 7.

Table 4: The OLS estimates for the replicates and the entire experiment.

Replicate	$\hat{\lambda}$	$\hat{\beta}$	$\hat{\gamma}$
1	0.5740	0.7901	-0.5801
2	0.5740	0.7901	-0.5801
All replicates	0.6942	1.3203	-0.4649

Table 5: The ML estimates for the replicates and the entire experiment.

Replicate	$\hat{\lambda}$	$\hat{\beta}$	$\hat{\gamma}$
1	1.9421	2.2892	-0.3645
2	1.9421	2.2892	-0.3645
All replicates	1.7398	1.8612	-0.2783

Table 6: The OLS estimates corresponding to each model.

Model	$\hat{\lambda}$	$\hat{\beta}$	$\hat{\gamma}$
1	0.5740	0.7901	-0.5801
2	0.6942	0.7901	-0.5801
3	0.5740	1.3203	-0.5801
4	0.5740	0.7901	-0.4649
5	0.5740	1.3203	-0.4649
6	0.6942	0.7901	-0.4649
7	0.6942	1.3203	-0.5801
8	0.6942	1.3203	-0.4649
9	----------	1.3203	-0.4649
10	0.6942	----------	-0.4649
11	----------	----------	-0.4649

Table 7: The ML estimates corresponding to each model.

Model	$\hat{\lambda}$	$\hat{\beta}$	$\hat{\gamma}$
1	1.9421	2.2892	-0.3645
2	1.7398	2.2892	-0.3645
3	1.9421	1.8612	-0.3645
4	1.9421	2.2892	-0.2783
5	1.9421	1.8612	-0.2783
6	1.7398	2.2892	-0.2783
7	1.7398	1.8612	-0.3645
8	1.7398	1.8612	-0.2783
9	----------	1.8612	-0.2783
10	1.7398	----------	-0.2783
11	----------	----------	-0.2783

Based on formula (17) and estimated values of parameters in Tables 6 and 7, the cumulative (Cum.) and estimated (Est.) response rates for the eleven models corresponding to OLS and ML estimation methods with respect to the different doses and each of the replicates are listed in Tables 8 – 18.

Table 8: The cumulative and estimated response rates for model 1.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	2.404101	2.845493	3.340886	3.434638
		Est.	2.404101	2.845493	3.340886	3.434638
	2	Cum.	2.841390	3.182045	3.544297	3.610806
		Est.	0.437289	0.336552	0.203411	0.176168
	3	Cum.	3.050501	3.336844	3.634439	3.688373
		Est.	0.209111	0.154799	0.090141	0.077567
	4	Cum.	3.178962	3.430196	3.687848	3.734192
		Est.	0.128461	0.093352	0.053409	0.045819
ML	1	Cum.	0.078596	0.188986	0.517438	0.634277
		Est.	0.078596	0.188986	0.517438	0.634277
	2	Cum.	1.438543	1.807514	2.349183	2.477006
		Est.	1.359947	1.618528	1.831744	1.842729
	3	Cum.	2.511752	2.786726	3.139709	3.216319
		Est.	1.073209	0.979212	0.790526	0.739313
	4	Cum.	3.065342	3.252998	3.482635	3.530986
		Est.	0.553590	0.466272	0.342925	0.314667

Table 9: The cumulative and estimated response rates for model 2.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	2.404101	2.845493	3.340886	3.434638
		Est.	2.404101	2.845493	3.340886	3.434638
	2	Cum.	2.920144	3.240773	3.578734	3.640474
		Est.	0.516042	0.395280	0.237847	0.205836
	3	Cum.	3.154496	3.412514	3.677785	3.725567
		Est.	0.234352	0.171742	0.099051	0.085093
	4	Cum.	3.293060	3.512069	3.734128	3.773813
		Est.	0.138564	0.099554	0.056343	0.048246
ML	1	Cum.	0.078596	0.188986	0.517438	0.634277
		Est.	0.078596	0.188986	0.517438	0.634277
	2	Cum.	1.233293	1.603806	2.168316	2.304605
		Est.	1.154698	1.414819	1.650878	1.670329
	3	Cum.	2.237081	2.546996	2.956067	3.046419
		Est.	1.003788	0.943190	0.787751	0.741814
	4	Cum.	2.812307	3.042434	3.329932	3.391267
		Est.	0.575226	0.495439	0.373865	0.344847

Table 10: The cumulative and estimated response rates for model 3.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	1.683987	2.242505	2.945641	3.087478
		Est.	1.683987	2.242505	2.945641	3.087478
	2	Cum.	2.237013	2.711633	3.256848	3.361378
		Est.	0.553026	0.469128	0.311207	0.273900
	3	Cum.	2.523914	2.939587	3.398848	3.485001
		Est.	0.286901	0.227953	0.142000	0.123623
	4	Cum.	2.707171	3.080696	3.484157	3.558886
		Est.	0.183256	0.141109	0.085309	0.073885

ML	1	Cum.	**0.308772**	**0.547016**	**1.054679**	**1.204352**
		Est.	0.308772	0.547016	1.054679	1.204352
	2	**Cum.**	2.053838	2.383412	2.827472	2.926824
		Est.	1.745066	1.836397	1.772793	1.722472
	3	**Cum.**	2.953519	3.160443	3.415927	3.470027
		Est.	0.899681	0.777030	0.588456	0.543204
	4	**Cum.**	3.362969	3.495770	3.654704	3.687698
		Est.	0.409450	0.335327	0.238776	0.217670

Table 11: The cumulative and estimated response rates for model 4.

Methods	**Time (days)**	**Death**	**Dose (Concentration)**			
			12.5	**25**	**75**	**100**
OLS	**1**	**Cum.**	2.024330	2.442092	2.974889	3.087225
		Est.	2.024330	2.442092	2.974889	3.087225
	2	**Cum.**	2.531455	2.871474	3.278536	3.361194
		Est.	0.507125	0.429382	0.303647	0.273968
	3	**Cum.**	2.783721	3.076065	3.416770	3.484849
		Est.	0.252266	0.204590	0.138234	0.123656
	4	**Cum.**	2.941641	3.201533	3.499726	3.558755
		Est.	0.157920	0.125468	0.082956	0.073906
ML	**1**	**Cum.**	0.030219	0.071206	0.205774	0.258548
		Est.	0.030219	0.071206	0.205774	0.258548
	2	**Cum.**	1.121741	1.402050	1.847991	1.961114
		Est.	1.091522	1.330844	1.642218	1.702566
	3	**Cum.**	2.242966	2.482557	2.814949	2.892084
		Est.	1.121226	1.080507	0.966958	0.930970
	4	**Cum.**	2.873197	3.044913	3.271800	3.322780
		Est.	0.630230	0.562355	0.456851	0.430696

Table 12: The cumulative and estimated response rates for model 5.

Methods	**Time (days)**	**Death**	**Dose (Concentration)**			
			12.5	**25**	**75**	**100**
OLS	**1**	**Cum.**	1.257336	1.729456	2.418533	2.575764
		Est.	1.257336	1.729456	2.418533	2.575764
	2	**Cum.**	1.838365	2.277410	2.852836	2.976131
		Est.	0.581029	0.547954	0.434304	0.400367
	3	**Cum.**	2.160411	2.559961	3.060234	3.164568
		Est.	0.322045	0.282551	0.207398	0.188437
	4	**Cum.**	2.372781	2.739914	3.187559	3.279455
		Est.	0.212371	0.179953	0.127325	0.114888
ML	**1**	**Cum.**	0.165599	0.289526	0.578216	0.670993
		Est.	0.165599	0.289526	0.578216	0.670993
	2	**Cum.**	1.746429	2.019727	2.418068	2.513547
		Est.	1.580830	1.730200	1.839852	1.842554
	3	**Cum.**	2.743473	2.931098	3.181269	3.237822
		Est.	0.997044	0.911371	0.763202	0.724274
	4	**Cum.**	3.224024	3.348344	3.508927	3.544469
		Est.	0.480551	0.417246	0.327657	0.306647

Table 13: The cumulative and estimated response rates for model 6.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	2.024330	2.442092	2.974889	3.087225
		Est.	2.024330	2.442092	2.974889	3.087225
	2	Cum.	2.625750	2.948579	3.331081	3.408272
		Est.	0.601420	0.506487	0.356192	0.321047
	3	Cum.	2.911396	3.177649	3.484037	3.544794
		Est.	0.285645	0.229070	0.152955	0.136522
	4	Cum.	3.083728	3.312842	3.572238	3.623177
		Est.	0.172332	0.135193	0.088202	0.078383
ML	1	Cum.	0.030219	0.071206	0.205774	0.258548
		Est.	0.030219	0.071206	0.205774	0.258548
	2	Cum.	0.926348	1.197367	1.645197	1.761590
		Est.	0.896129	1.126161	1.439423	1.503042
	3	Cum.	1.942201	2.204655	2.579251	2.667817
		Est.	1.015853	1.007288	0.934055	0.906227
	4	Cum.	2.581358	2.787524	3.065734	3.129127
		Est.	0.639157	0.582869	0.486483	0.461310

Table 14: The cumulative and estimated response rates for model 7.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	1.683987	2.242505	2.945641	3.087478
		Est.	1.683987	2.242505	2.945641	3.087478
	2	Cum.	2.343391	2.797223	3.310801	3.408445
		Est.	0.659404	0.554718	0.365161	0.320967
	3	Cum.	2.671861	3.053760	3.468017	3.544929
		Est.	0.328471	0.256536	0.157216	0.136484
	4	Cum.	2.874345	3.206684	3.558781	3.623290
		Est.	0.202483	0.152925	0.090764	0.078361
ML	1	Cum.	0.308772	0.547016	1.054679	1.204352
		Est.	0.308772	0.547016	1.054679	1.204352
	2	Cum.	1.857755	2.204706	2.683607	2.792383
		Est.	1.548983	1.657690	1.628928	1.588031
	3	Cum.	2.738779	2.980466	3.284334	3.349423
		Est.	0.881024	0.775760	0.600727	0.557041
	4	Cum.	3.179323	3.346567	3.549439	3.591918
		Est.	0.440544	0.366101	0.265105	0.242494

Table 15: The cumulative and estimated response rates for model 8.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	1.257336	1.729456	2.418533	2.575764
		Est.	1.257336	1.729456	2.418533	2.575764
	2	Cum.	1.956239	2.382298	2.930965	3.047312
		Est.	0.698902	0.652842	0.512433	0.471548
	3	Cum.	2.331474	2.705271	3.163314	3.257623
		Est.	0.375235	0.322974	0.232348	0.210311
	4	Cum.	2.570807	2.903747	3.300597	3.380971
		Est.	0.239333	0.198476	0.137283	0.123347

ML	1	Cum.	**0.165599**	**0.289526**	**0.578216**	**0.670993**
		Est.	0.165599	0.289526	0.578216	0.670993
	2	**Cum.**	1.541606	1.822300	2.241629	2.343765
		Est.	1.376007	1.532774	1.663412	1.672771
	3	**Cum.**	2.497721	2.712837	3.005015	3.071877
		Est.	0.956115	0.890537	0.763387	0.728112
	4	**Cum.**	3.006615	3.161033	3.363250	3.408418
		Est.	0.508895	0.448196	0.358235	0.336542

Table 16: The cumulative and estimated response rates for model 9.

Methods	**Time (days)**	**Death**	**Dose (Concentration)**			
			12.5	**25**	**75**	**100**
OLS	**1**	**Cum.**	1.257336	1.729456	2.418533	2.575764
		Est.	1.257336	1.729456	2.418533	2.575764
	2	**Cum.**	2.242620	2.630175	3.110327	3.209837
		Est.	0.985284	0.900720	0.691794	0.634073
	3	**Cum.**	2.719718	3.024659	3.382392	3.454156
		Est.	0.477097	0.394484	0.272066	0.244319
	4	**Cum.**	2.995076	3.243563	3.527224	3.583204
		Est.	0.275358	0.218904	0.144831	0.129047
ML	**1**	**Cum.**	0.165599	0.289526	0.578216	0.670993
		Est.	0.165599	0.289526	0.578216	0.670993
	2	**Cum.**	0.813876	1.076153	1.520811	1.638284
		Est.	0.648278	0.786627	0.942594	0.967290
	3	**Cum.**	1.383754	1.667002	2.099279	2.206037
		Est.	0.569878	0.590849	0.578468	0.567753
	4	**Cum.**	1.804302	2.074756	2.466423	2.559909
		Est.	0.420548	0.407754	0.367144	0.353872

Table 17: The cumulative and estimated response rates for model 10.

Methods	**Time (days)**	**Death**	**Dose (Concentration)**			
			12.5	**25**	**75**	**100**
OLS	**1**	**Cum.**	1.726636	2.176265	2.776120	2.905998
		Est.	1.726636	2.176265	2.776120	2.905998
	2	**Cum.**	2.379896	2.745864	3.191711	3.283192
		Est.	0.653260	0.569599	0.415591	0.377193
	3	**Cum.**	2.703213	3.011350	3.373453	3.446169
		Est.	0.323317	0.265486	0.181743	0.162978
	4	**Cum.**	2.901938	3.170166	3.479111	3.540410
		Est.	0.198724	0.158817	0.105658	0.094241
ML	**1**	**Cum.**	1.041184	1.318489	1.766212	1.880868
		Est.	1.041184	1.318489	1.766212	1.880868
	2	**Cum.**	2.673280	2.869120	3.131583	3.191115
		Est.	1.632096	1.550631	1.365371	1.310247
	3	**Cum.**	3.278086	3.394573	3.544546	3.577668
		Est.	0.604806	0.525452	0.412964	0.386553
	4	**Cum.**	3.545344	3.621192	3.717353	3.738372
		Est.	0.267258	0.226620	0.172806	0.160704

Table 18: The cumulative and estimated response rates for model 11.

Methods	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
OLS	1	Cum.	1.726636	2.176265	2.776120	2.905998
		Est.	1.726636	2.176265	2.776120	2.905998
	2	Cum.	2.628030	2.950434	3.332338	3.409398
		Est.	0.901394	0.774169	0.556219	0.503399
	3	Cum.	3.023015	3.265456	3.541490	3.595879
		Est.	0.394984	0.315023	0.209152	0.186482
	4	Cum.	3.242240	3.435365	3.650939	3.692911
		Est.	0.219226	0.169909	0.109448	0.097032
ML	1	Cum.	1.041184	1.318489	1.766212	1.880868
		Est.	1.041184	1.318489	1.766212	1.880868
	2	Cum.	2.040768	2.296510	2.657978	2.742895
		Est.	0.999584	0.978020	0.891766	0.862027
	3	Cum.	2.553970	2.763114	3.045937	3.110470
		Est.	0.513202	0.466605	0.387959	0.367576
	4	Cum.	2.857109	3.030848	3.260662	3.312337
		Est.	0.303139	0.267734	0.214724	0.201867

The values of MSE for each model can be determined now using the estimated values in Tables 8–18 and the observed values for response rates of breast cancer cells treated physically and environmentally in Tables 2 and 3. The results according to each estimating method are given in Tables 19 and 20, where the bold numbers represent the associated values of the best model.

Table 19: The MSE value for each model related to OLS method.

Model	Physical Experiment	Green Experiment
1	1.9766	1.9527
2	1.8904	1.8609
3	1.2575	1.2476
4	1.3923	1.3779
5	0.7257	0.7307
6	1.3276	1.3055
7	1.1988	1.1798
8	0.6853	0.6787
9	0.6589	**0.6292**
10	0.9996	0.9835
11	0.9573	0.9240

Table 20: The MSE value for each model related to ML method.

Model	Physical Experiment	Green Experiment
1	0.4401	0.3781
2	0.3122	0.2688
3	0.4833	0.4097
4	0.3658	0.3214
5	0.4381	0.3751
6	0.2606	0.2366
7	0.3629	0.3031
8	0.3146	0.2672
9	**0.0960**	0.1229
10	0.4829	0.4217
11	0.3117	0.2912

Table 19 demonstrates that the MSE values for the green experiment are lower than those for the physical experiment, with the exception of model 5, and the same holds true for the MSE values in Table 20 with all models except model 9. Tables 19 and 20 show that the MSE values of

ML of all models are lower than those of the OLS. For the OLS method related to the green experiment, model 9 is the best model with a value of MSE equal to 0.6292 and the same model is the best for the ML method related to the physical experiment with a value of MSE equal to 0.0960. Finally, the estimates of the LD_{50} for the best model can be calculated by using formula (19), the results are listed in Table 21. According to Table 21, the LD_{50} estimates of the green and physical treatments, related respectively to OLS and ML methods, exhibit a decreasing dose-time relationship over four days.

Table 21: The estimates of the LD_{50} for the best model.

Days	Model 9	
	OLS	ML
	Green Experiment	Physical Experiment
1	37.6500818	2995.055168
2	8.47715918	248.1592054
3	3.54387179	57.80846087
4	1.90868716	20.56155489

Conclusions

The most important conclusions are:

1. For biological experiments with multivariate quantal responses, IW is used to achieve the possibility of using the probability models of the response time to create a model of the response relationship with natural logarithm dose and time.
2. The mathematical formulas for the OLS and ML estimators were obtained for the unknown parameters. Because these estimations could not be derived directly, the Newton-Raphson approach is utilized as one of the iterative techniques.
3. The LD_{50} can be estimated through the cumulative function of the probability model to evaluate the degree of degree of response and to establish the highest and lowest concentrations that can result in 50% lethal effects over four days. By using these findings, one can determine the dose concentrations at which there are no deadly side effects. Thus, depending on the considered model, the approved method for estimating LD_{50} provides the possibility of obtaining multiple estimates with successive periods, through which several effective concentrations of 50% can be obtained in the experimental units. Thus, this method is more flexible than the traditional methods that depend on calculating only one estimated value of LD_{50} at a specific time.
4. Based on the statistical criterion MSE, model 9 of the cumulative function is the best, and that represents the best evidence that the experiment's replications are not important. The LD_{50} estimates of the green and physical experiments related to the two estimation methods exhibited a decreasing dose-time relationship over four days.
5. Further, related to the two estimation methods, when the last three models are excluded, the green experiment with the eighth and sixth models respectively has the lowest value for MSE, demonstrating the superiority of the green experiment over the physical experiment.

Based on the above conclusions, for future work, below are some recommendations:

6. Using the same procedure to estimate the LD_{50} to determine the toxicity of pesticides through use for insects or plant protection in multivariate quantal response bioassays.
7. Utilizing other probability models to construct models for estimating the LD_{50}, such as Lomax, Logistic, or Gamma models.
8. Utilizing other statistical estimation methods to estimate the unknown parameters, such as moments, rank set sampling, or Bayesian methods.

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صيغة إحصائية جديدة لتقدير الجرعة المميتة الوسيطة لسرطان الثدي على أساس أنموذج معكوس ويبل

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المستخلص

في هذا البحث ، تم تقدير الجرعة المميتة الوسيطة لتجربة بيولوجية متعددة المتغيرات ثنائية التكرار من خلال صيغة إحصائية جديدة تتعلق بأفضل أنموذج بين أحد عشر أنموذجًا تم تصميمها لوصف العلاقة بين الجرعة والاستجابة والوقت استنادًا إلى معكوس ويبل . ركزت التجربة البيولوجية الحقيقية على اعتماد البيانات الحقيقية لعلاج سرطان الثدي بيولوجيًا باعتماد سيلينيد الزنك العلاجي، الذي يتم إنتاجه إما عن طريق البلازما فيزيائيا أو عن طريق اعتماد مستخلص نباتي بيئي (نبات كالجان). تم تقدير المعلمات المجهولة المرتبطة بالنماذج الأحد عشر بطريقتين تقليديتين للتقدير: المربعات الصغرى الاعتيادية والامكان الاعظم. ولكون هذه التقديرات لا يمكن تحديدها بشكل مباشر، تم توظيف تقنية نيوتن-رافسون التكرارية . تم اعتماد متوسط مربعات الخطأ لاختيار الانموذج الأفضل . ثم، لنقاط زمنية متتالية، تم احتساب الجرعة المميتة الوسيطة لسرطان الثدي .اظهرت النتائج بوضوح أن قيم متوسط مربع الخطأ ذات الامكان الاعظم تكون دائمًا أقل من قيم المربعات الصغرى الاعتيادية، واظهرت الجرعة المميتة الوسيطة علاقة متناقصة (عكسية) بمرور الزمن .علاوة على ذلك، فإن الاسلوب الجديد لقياس الجرعة المميتة الوسيطة قد سمح بعدة تقديرات مع فترات زمنية متتالية، مما يسمح بعدة تركيزات فعالة بنسبة 50٪ في الوحدات التجريبية.

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