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Estimating the Median Lethal Dose of Breast Cancer with Modified Weibull Statistical Model

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Abstract
In this paper, based on a linear relationship between the natural logarithms of the scale parameter and dose, nineteen models are constructed using the modified Weibull statistical model to describe the relationship of dose-response and time for multivariate dual-response life experiments with two-replicate. The real biological data set is considered to evaluate the response rates of breast cancer cells treated with the therapeutic zinc selenide prepared in two different ways (physically and environmentally/organically). The unknown parameters are estimated using two estimation methods. The mean square error is used to select the best model. The median lethal dose is then determined on the basis of a new formula at successive times. The best models for each estimation method show that the experiment's replications are unimportant and that the median lethal dose estimates exhibit a decreasing dose-time relationship over the days.
Keywords: biological experiment, median lethal dose, modified Weibull, traditional estimation methods.

1. Introduction
The standard Weibull model with two parameters [1] is used in numerous disciplines. Various applications of the Weibull model include tidal heights, treatment efficiency, temperature fluctuations, discharge inference, wind speed, brittle material, reliability growth, raindrop size, latent failures of electronic products, and damage in laminated composites. Interested readers can find further applications in [2,3]. However, only increasing, decreasing, or constant risk functions are possible for the Weibull distribution. Therefore, it cannot be used to simulate lifetime data with a bathtub-shaped hazard function, such as human mortality and machine life cycles [4]. For many years, several researchers (see [5–7]), have developed various modifications and extensions of the Weibull model by adding additional parameters. Additionally, for more recent references, one can see [8-12]. In this paper, the modified version proposed by [5] is considered to construct nineteen models describing the relationship of dose, response, and time for multivariate dual-response life experiments with two replicates.

The probability density function (PDF) and cumulative function (CF) of the modified Weibull (MW) model, with scale parameter (α) and shape parameters (β, λ), are given respectively by [5]

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

$$F(t; \alpha, \beta, \lambda) = 1 - e^{-\alpha t^{\beta} e^{\lambda t}} \qquad ;\; t \geq 0, \alpha > 0\,, \beta, \lambda \geq 0 \tag{2}$$

For a biological experiment, suppose there is a linear relationship between the natural–logarithms of the scale parameter and dose, i.e. $\ln(\alpha) = \gamma + \delta \ln(d)$ (see [13,14]). So, the scale parameter is equivalent to

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

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

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

$$F(t_j; \gamma, \delta, \beta, \lambda) = 1 - e^{-t_j^{\beta} e^{\gamma + \delta \ln(d_i) + \lambda t_j}} \;;\; t \geq 0, -\infty < \gamma < \infty, \delta \neq 0\,, \beta, \lambda \geq 0 \tag{5}$$

In statistics, the evaluation of the nature, constitution, or potency of a material/or of a process using the reaction that results from its application to living matter is known as a statistical analysis of bioassays. An assay is thus a type of biological experiment, but the focus is on comparing the magnitudes of different treatments' effects. There are two types of biological experiments: univariate quantal responses, which are reliant on the dose-response relationship, and multivariate quantal responses, which are dependent on the dose-response relationship over time. The calculation of effective doses, particularly the median lethal dose (LD_{50}), is one of the most important applications of this type of experiment.

As a pioneering work, Trevan (see [15]) developed the LD_{50} test to determine the dose of a test substance that results in 50% mortality in a particular species of animals. Before conducting additional toxicity studies on a chemical, this test is typically the first one to be performed. It is employed to calculate the possible risks that chemicals may pose to people. Depending on the chemical being tested, the non-lethal acute effects may appear as signs of toxicity even though death is its primary endpoint. Nowadays, numerous studies have been introduced to do so. For example, in 2018, [16] used probit-log(dose) regression models and the maximum likelihood method to calculate lethal doses of toxicants at various significance levels, as well as the lethal dose ratio for two toxicants. In 2019, [17] investigated probation and the impact of a chemical compound using dose-response studies and non-linear regression to assess efficacy metrics. They presented a Bayesian inference framework for analyzing and comparing dose-response experiments. In 2020, [18] determined the LD_{50} of Medemia argun seed's crude ethanolic and the dose-response curve of several doses of the extract against carbon tetrachloride-treated animals to assess its hepatotoxicity. In 2021, [19] determined LD_{50} and acute toxicity of the formulation Cytoreg, an ionic mixture of strong and weak acids. Also, in 2021 [20] used the exponential model to assess the dose-response relationship and calculated the LD_{50} of the poison for disinfectant jungles (Roanstar) on a group of fish. Further, in 2021 [21] determined the LD_{50} of zinc chloride administered intraperitoneally to albino rats at concentrations ranging from $10(10)100$ mg/kg body weight of the experimental animals. In 2022, [22] investigated the toxic effect of a mixture of three pesticides (cypermethrin, mancozeb, and metalaxyl) on reproduction and oxidative stress parameters in male Wistar rats. In 2023, [23] examined the 25, 50, and 75%

lethal doses of gamma radiation on the survival rate, leaves, shoots, and root morphometric features after gamma irradiation. The statistical significance of the differences between the mean values of four replications was investigated using a one-way analysis of variance. Further, by revising [24-28], one can see more details about dose-response and lethal dose. This work is focused on modeling the multivariate quantal response by using the modified Weibull statistical model to predict LD_{50} of breast cancer based on cumulative function. The remainder of this paper is organized as follows: Section 2 introduces parameter estimators based on two estimating methods. Sections 3 and 4 provide the initial values of the parameters as well as the cumulative affected numbers. The best model and median lethal dose estimation are found in Section 5. Section 6 discusses real biological applications and their outcomes.

2 Parameters Estimators

2.1 Ordinary Least Squares Parameters Estimators

Let $t_1, \dots, t_n$ be a random sample from MW model with doses $d_i(d_1, \dots, d_k)$, then the ordinary least squares (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 and empirical CF for $\mathrm{j} = 1, \dots, \mathrm{n}$ respectively given as $\hat{F}\left(t_j\right) = F\left(t_j; \hat{\gamma}, \hat{\delta}, \hat{\beta}, \hat{\lambda}\right) = 1 - e^{-t_j^{\hat{\beta}}\, e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}$ and $F\left(t_j\right) = F_j = \frac{j - 0.5}{n}$. Now $\sum_{j=1}^{n} \epsilon_j^2 = \sum_{j=1}^{n} \left(1 - e^{-t_j^{\hat{\beta}}\, e^{\hat{\gamma} + \hat{\delta}\, ln(d_i) + \hat{\lambda} t_j}} - F_j\right)^2$ and then

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

where $S_j = 1 - F_j = \frac{n - j + 0.5}{n}$.

Let $z_1(\gamma),\ z_2(\delta), z_3(\beta)$ and $z_4(\lambda)$ represent the partial derivatives of $\sum_{j=1}^{n} \epsilon_j^2$ in (6) to $\gamma, \delta, \beta, \lambda$ and set it equal to zero, as follows

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

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

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

$$z_4(\lambda) = 2 \sum_{j=1}^{n} t_j^{\hat{\beta}+1}\, e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j - t_j^{\hat{\beta}}\, e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}} \left(S_j - e^{-\, t_j^{\hat{\beta}}\, e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right) = 0 \tag{10}$$

Noticing that Equations (7) to (10) are non–linear and difficult to solve in traditional methods. By iterative processes, the four $(\hat{\gamma}, \hat{\delta}, \hat{\beta}, \hat{\lambda})$ OLS estimates can be obtained respectively. With the iterative Newton-Raphson method, the Jacobin matrix is used with iteration (s), as shown below

$$\begin{bmatrix} \gamma_{s+1} \\ \delta_{s+1} \\ \beta_{s+1} \\ \lambda_{s+1} \end{bmatrix} = \begin{bmatrix} \gamma_s \\ \delta_s \\ \beta_s \\ \lambda_s \end{bmatrix} - J_s^{-1} \begin{bmatrix} z_1(\gamma) \\ z_2(\delta) \\ z_3(\beta) \\ z_4(\lambda) \end{bmatrix} \tag{11}$$

The OLS estimated values can be obtained iteratively from (11) 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 $\gamma_0, \delta_0, \beta_0, \lambda_0$ represent the initial values, and the Jacobin matrix must be a non-singular symmetric matrix J_s to obtain its inverse, where

$J_s = \begin{bmatrix} \frac{\partial z_1(\gamma)}{\partial\gamma} & \frac{\partial z_1(\gamma)}{\partial\delta} & \frac{\partial z_1(\gamma)}{\partial\beta} & \frac{\partial z_1(\gamma)}{\partial\lambda} \\ \frac{\partial z_2(\delta)}{\partial\gamma} & \frac{\partial z_2(\delta)}{\partial\delta} & \frac{\partial z_2(\delta)}{\partial\beta} & \frac{\partial z_2(\delta)}{\partial\lambda} \\ \frac{\partial z_3(\beta)}{\partial\gamma} & \frac{\partial z_3(\beta)}{\partial\delta} & \frac{\partial z_3(\beta)}{\partial\beta} & \frac{\partial z_3(\beta)}{\partial\lambda} \\ \frac{\partial z_4(\lambda)}{\partial\gamma} & \frac{\partial z_4(\lambda)}{\partial\delta} & \frac{\partial z_4(\lambda)}{\partial\beta} & \frac{\partial z_4(\lambda)}{\partial\lambda} \end{bmatrix}$, and the partial derivatives of Equations (7) to (10) concerning unknown parameters are

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

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

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

$$\frac{\partial z_1(\gamma)}{\partial\lambda} = \frac{\partial z_4(\lambda)}{\partial\gamma} = 2\sum_{j=1}^{n} S_j\, t_j^{\hat\beta+1}\, e^{\hat\gamma+\hat\delta\ln(d_i)+\hat\lambda t_j - t_j^{\hat\beta}\, e^{\hat\gamma+\hat\delta\ln(d_i)+\hat\lambda t_j}} \left(1 - t_j^{\hat\beta} e^{\hat\gamma+\hat\delta\, ln(d_i)+\hat\lambda t_j}\right)$$
$$-2\sum_{j=1}^{n} t_j^{\hat\beta+1}\, e^{\hat\gamma+\hat\delta\ln(d_i)+\hat\lambda t_j - 2t_j^{\hat\beta}\, e^{\hat\gamma+\hat\delta\ln(d_i)+\hat\lambda t_j}} \left(1 - 2t_j^{\hat\beta} e^{\hat\gamma+\hat\delta\, ln(d_i)+\hat\lambda t_j}\right)$$

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

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

$$\frac{\partial z_2(\delta)}{\partial \lambda}=\frac{\partial z_4(\lambda)}{\partial \delta}=2\ln(d_i)\sum_{j=1}^{n} S_j t_j^{\hat{\beta}+1}\; e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\left(1-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}\right)-2\ln(d_i)\sum_{j=1}^{n} t_j^{\hat{\beta}+1}\, e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-2t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}(1-2t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j})$$

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

$$\frac{\partial z_3(\beta)}{\partial \lambda}=\frac{\partial z_4(\lambda)}{\partial \beta}=2\sum_{j=1}^{n} S_j\, t_j^{\hat{\beta}+1}\ln(t_j)\; e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\left(1-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}\right)-2\sum_{j=1}^{n} t_j^{\hat{\beta}+1}\ln(t_j)\; e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-2t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\left(1-2t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}\right)$$

$$\frac{\partial z_4(\lambda)}{\partial \lambda}=2\sum_{j=1}^{n} S_j\, t_j^{\hat{\beta}+2}\, e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\left(1-t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}\right)-2\sum_{j=1}^{n} t_j^{\hat{\beta}+2}\, e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j-2\,t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\left(1-2t_j^{\hat{\beta}}e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}\right)$$

2.2 Maximum Likelihood Parameters Estimators

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

$$L=\prod_{j=1}^{n}\left(e^{\gamma+\delta\ln(d_i)}(\beta+\lambda t_j)t_j{}^{\beta-1}\, e^{\lambda t_j-e^{\gamma+\delta\ln(d_i)}t_j^{\beta}e^{\lambda t_j}}\right) \tag{12}$$

Take the natural–logarithm of the likelihood function

$$\ln L=n\gamma+n\delta\ln(d_i)+\sum_{j=1}^{n}\ln(\beta+\lambda t_j)+\beta\sum_{j=1}^{n}\ln(t_j)-\sum_{j=1}^{n}\ln(t_j)+\lambda\sum_{j=1}^{n}t_j-e^{\gamma+\delta\ln(d_i)}\sum_{j=1}^{n}t_j^{\beta}e^{\lambda t_j} \tag{13}$$

Let $g_1(\gamma)$, $g_2(\delta)$, $g_3(\beta)$ and $g_4(\lambda)$ represent the partial derivatives of $\ln L$ in (13) to $\gamma,\delta,\beta,\lambda$ and set it equal to zero, as follows

$$g_1(\gamma) = \frac{\partial \ln L}{\partial \gamma} = n - \sum_{j=1}^{n} t_j^{\hat{\beta}} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j} = 0 \tag{14}$$

$$g_2(\delta) = \frac{\partial \ln L}{\partial \delta} = n\ln(d_i) - \ln(d_i)\sum_{j=1}^{n} t_j^{\hat{\beta}} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j} = 0 \tag{15}$$

$$g_3(\beta) = \frac{\partial \ln L}{\partial \beta} = \sum_{j=1}^{n} \frac{1}{\hat{\beta}+\hat{\lambda}t_j} + \sum_{j=1}^{n} \ln(t_j) - \sum_{j=1}^{n} t_j^{\hat{\beta}} \ln(t_j)\, e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j} = 0 \tag{16}$$

$$g_4(\lambda) = \frac{\partial \ln L}{\partial \lambda} = \sum_{j=1}^{n} \frac{t_j}{\hat{\beta}+\hat{\lambda}t_j} + \sum_{j=1}^{n} t_j - \sum_{j=1}^{n} t_j^{\hat{\beta}+1} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j} = 0 \tag{17}$$

The maximum likelihood (ML) estimated values of four parameters can be obtained by solving the nonlinear Equations (14) to (17) numerically through the iterative Newton-Raphson method as in (18) until convergence occurs,

$$\begin{bmatrix}\gamma_{s+1}\\ \delta_{s+1}\\ \beta_{s+1}\\ \lambda_{s+1}\end{bmatrix} = \begin{bmatrix}\gamma_{s}\\ \delta_{s}\\ \beta_{s}\\ \lambda_{s}\end{bmatrix} - J_s^{-1}\begin{bmatrix}g_1(\gamma)\\ g_2(\delta)\\ g_3(\beta)\\ g_4(\lambda)\end{bmatrix} \tag{18}$$

where $J_s = \begin{bmatrix} \frac{\partial g_1(\gamma)}{\partial\gamma} & \frac{\partial g_1(\gamma)}{\partial\delta} & \frac{\partial g_1(\gamma)}{\partial\beta} & \frac{\partial g_1(\gamma)}{\partial\lambda} \\ \frac{\partial g_2(\delta)}{\partial\gamma} & \frac{\partial g_2(\delta)}{\partial\delta} & \frac{\partial g_2(\delta)}{\partial\beta} & \frac{\partial g_2(\delta)}{\partial\lambda} \\ \frac{\partial g_3(\beta)}{\partial\gamma} & \frac{\partial g_3(\beta)}{\partial\delta} & \frac{\partial g_3(\beta)}{\partial\beta} & \frac{\partial g_3(\beta)}{\partial\lambda} \\ \frac{\partial g_4(\lambda)}{\partial\gamma} & \frac{\partial g_4(\lambda)}{\partial\delta} & \frac{\partial g_4(\lambda)}{\partial\beta} & \frac{\partial g_4(\lambda)}{\partial\lambda} \end{bmatrix}$, and the partial derivatives for unknown parameters are

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

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

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

$$\frac{\partial g_1(\gamma)}{\partial \lambda} = \frac{\partial g_4(\lambda)}{\partial \gamma} = -\sum_{j=1}^{n} t_j^{\hat{\beta}+1} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}$$

$$\frac{\partial g_2(\delta)}{\partial \delta} = -(\ln(d_i))^2 \sum_{j=1}^{n} t_j^{\hat{\beta}} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}$$

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

$$\frac{\partial g_2(\delta)}{\partial \lambda} = \frac{\partial g_4(\lambda)}{\partial \delta} = -\ln(d_i)\sum_{j=1}^{n} t_j^{\hat{\beta}+1} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}$$

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

$$\frac{\partial g_3(\beta)}{\partial \lambda} = \frac{\partial g_4(\lambda)}{\partial \beta} = -\sum_{j=1}^{n} \frac{t_j}{\left(\hat{\beta}+\hat{\lambda}t_j\right)^2} - \sum_{j=1}^{n} t_j^{\hat{\beta}+1} \ln(t_j)\; e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}$$

$$\frac{\partial g_4(\lambda)}{\partial \lambda} = -\sum_{j=1}^{n} \frac{t_j^2}{\left(\hat{\beta}+\hat{\lambda}t_j\right)^2} - \sum_{j=1}^{n} t_j^{\hat{\beta}+2}\; e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}$$

3. The Initial Values of the Parameters

It is necessary to indicate the possibility of calculating the initial values of parameters $(\gamma_0, \delta_0, \beta_0, \lambda_0)$ 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 (5) will be $F(t_j) = F(t_j; \gamma, \delta, \beta, \lambda) = 1 - e^{-t_j^{\beta} e^{\gamma+\delta\ln(d_i)+\lambda t_j}}$, 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 $Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3$, then $Y = \ln\left(-\ln\left(1 - F(t_j)\right)\right)$, $X_1 = t_j$, $X_2 = \ln(t_j)$, $X_3 = \ln(d_i)$ with coefficients $b_0 = \gamma$, $b_1 = \lambda, b_2 = \beta$ and $b_3 = \delta$. Thus, the initial values $(\gamma_0, \delta_0, \beta_0, \lambda_0)$ can be attained easily now by using the OLS method that is available in different statistical programs such as SPSS.

4. The Cumulative Affected Numbers

Repeating the biological experiment is vital to confirm that an observed result represents a natural occurrence (see [29]). 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 estimates of C_{ijl} can be obtained based on the CF in (5) by the following formula:

$$\hat{C}_{ijl} = n_{il}\,\hat{F}(t_j) = n_{il}\,\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}+\hat{\delta}\ln(d_i)+\hat{\lambda}t_j}}\right) \tag{19}$$

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

Since the MW contains four 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' cumulative function estimator in **Table1.**

5. Best 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 the number of model parameters (p), the best model can be chosen with the lowest value of the mean square error (MSE) criterion, where

$$MSE(\hat{u}) = \frac{1}{N-p}\sum_{i,j,l}\left(u_{ijl} - \hat{u}_{ijl}\right)^2 ; i = 1, \dots, k\,; j = 1, \dots, n\,; l = 1, \dots, r \tag{20}$$

The median lethal dose (LD_{50}) for the best model can be estimated by making the CF with considered estimated values equal to 0.50, $\hat{F}(t_j) = 0.50$, i.e. $1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}+\hat{\delta}\ln(d)+\hat{\lambda}t_j}} = 0.50$. After taking the double logarithm for two-sided, we get, $\hat{\gamma} + \hat{\delta}\ln(d) + \hat{\beta}\ln(t_j) + \hat{\lambda}t_j = \ln(-\ln(0.50))$, and then with $x_j = \ln(d)$, the LD_{50} is equal to

$$LD_{50} = d = e^{x_j} \tag{21}$$

where

$$x_j = \frac{-\hat{\gamma} - \hat{\beta}\ln(t_j) - \hat{\lambda}t_j - 0.366513}{\hat{\delta}} \tag{22}$$

Table 1. The MW model's cumulative function estimators

Model	Cumulative function estimator
1	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma}_l + \hat{\delta}_l \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
2	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma}_l + \hat{\delta}_l \ln(d_i) + \hat{\lambda} t_j}}\right)$
3	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}_l + \hat{\delta}_l \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
4	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma}_l + \hat{\delta} \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
5	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma} + \hat{\delta}_l \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
6	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}_l + \hat{\delta}_l \ln(d_i) + \hat{\lambda} t_j}}\right)$
7	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma}_l + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right)$
8	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma} + \hat{\delta}_l \ln(d_i) + \hat{\lambda} t_j}}\right)$
9	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}_l + \hat{\delta} \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
10	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma} + \hat{\delta}_l \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
11	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
12	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma}_l + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right)$
13	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma} + \hat{\delta}_l \ln(d_i) + \hat{\lambda} t_j}}\right)$
14	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}_l} e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right)$
15	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda}_l t_j}}\right)$
16	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right)$
17	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j^{\hat{\beta}} e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + t_j}}\right) ; \lambda = 1$
18	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + \hat{\lambda} t_j}}\right) ;\ \beta = 1$
19	$\hat{C}_{ijl} = n_{il}\left(1 - e^{-t_j e^{\hat{\gamma} + \hat{\delta} \ln(d_i) + t_j}}\right) ; \lambda = 1 ; \beta = 1$

6. Real Biological Application

In this section, the nineteen models listed in Table 1 are evaluated, and the median lethal dose at various period of the best model is determined using two-replicate multivariate dual-response biological experiments. The real application 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 treatment) using plasma and second, environmentally (green treatment) using plant extract (Kalgan plant) (for more details see [30]). Tables 2 and 3 represent the response rates of breast cancer cells for the two ways of applying ZnSe on cells for exposure times 24 and 72 hours with different concentrations of ZnSe $(\mathrm{mg/ml})$ ranging between $(12.5 - 100)$ percent.

Table 2. Response rates of breast cancer cells treated physically

Rep.	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	0.5849	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 environmentally

Rep.	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

By using the least squares method as described in section 3, the initial values for the four parameters are $\gamma_0 = -1.671, \delta_0 = -0.081, \beta_0 = 0.734$, and $\lambda_0 = 0.375$. Now, based on the initial values and $\varepsilon = 0.001$, with a program written by MATLAB (R2018b), the iterative Newton-Raphson method with Equations (11) and (18) are used to calculate the OLS and ML estimates of four parameters. **Tables 4–7** summarized the obtained estimates for each replicate and the entire experiment, as well as the obtained estimates corresponding to each model and each estimation method.

Table 4. The OLS estimates for each replicate and entire experiment

Rep.	$\hat{\boldsymbol{\gamma}}$	$\hat{\boldsymbol{\delta}}$	$\hat{\boldsymbol{\beta}}$	$\hat{\boldsymbol{\lambda}}$
1	-1.1454	-0.1827	0.5234	0.3825
2	-1.1454	-0.1827	0.5234	0.3825
Experiment	-2.1507	0.0298	0.6183	0.3787

Table 5. The OLS estimates of 2nd experiment corresponding to each model

Models	$\hat{\gamma}$	$\hat{\delta}$	$\hat{\beta}$	$\hat{\lambda}$
1	-1.1454	-0.1827	0.5234	0.3825
2	-1.1454	-0.1827	0.5234	0.3787
3	-1.1454	-0.1827	0.6183	0.3825
4	-1.1454	0.0298	0.5234	0.3825
5	-2.1507	-0.1827	0.5234	0.3825
6	-1.1454	-0.1827	0.6183	0.3787
7	-1.1454	0.0298	0.5234	0.3787
8	-2.1507	-0.1827	0.5234	0.3787
9	-1.1454	0.0298	0.6183	0.3825
10	-2.1507	-0.1827	0.6183	0.3825
11	-2.1507	0.0298	0.5234	0.3825
12	-1.1454	0.0298	0.6183	0.3787
13	-2.1507	-0.1827	0.6183	0.3787
14	-2.1507	0.0298	0.5234	0.3787
15	-2.1507	0.0298	0.6183	0.3825
16	-2.1507	0.0298	0.6183	0.3787
17	-2.1507	0.0298	0.6183	---
18	-2.1507	0.0298	---	0.3787
19	-2.1507	0.0298	---	---

Table 6. The ML estimates for each replicate and entire experiment

Rep.	$\hat{\gamma}$	$\hat{\delta}$	$\hat{\beta}$	$\hat{\lambda}$
1	- 0.3095	- 0.6942	1.6349	0.3374
2	- 0.3095	- 0.6942	1.6349	0.3374
Experiment	-13.2077	2.4845	1.6349	0.3374

Table 7. The ML estimates of 2nd experiment corresponding to each model

Models	$\hat{\gamma}$	$\hat{\delta}$	$\hat{\beta}$	$\hat{\lambda}$
1	- 0.30950	- 0.6942	1.6349	0.3374
2	- 0.30950	- 0.6942	1.6349	0.3374
3	- 0.30950	- 0.6942	1.6349	0.3374
4	- 0.30950	2.48450	1.6349	0.3374
5	-13.2077	- 0.6942	1.6349	0.3374
6	- 0.30950	- 0.6942	1.6349	0.3374
7	- 0.30950	2.48450	1.6349	0.3374
8	-13.2077	- 0.6942	1.6349	0.3374
9	- 0.30950	2.48450	1.6349	0.3374
10	-13.2077	- 0.6942	1.6349	0.3374
11	-13.2077	2.48450	1.6349	0.3374
12	- 0.30950	2.48450	1.6349	0.3374
13	-13.2077	2.48450	1.6349	0.3374
14	-13.2077	2.48450	1.6349	0.3374
15	-13.2077	2.48450	1.6349	0.3374
16	-13.2077	2.48450	1.6349	0.3374
17	-13.2077	2.48450	1.6349	---
18	-13.2077	2.48450	---	0.3374
19	-13.2077	2.48450	---	---

Further, based on formula (19) and estimated values of parameters in **Tables 5** and **7**, the cumulative and estimated response rates for the nineteen models corresponding to OLS and ML estimation methods with respect to the different doses and replicates are calculated and listed in **Tables 8** and **9**.

Table 8. The cumulative and estimated response rates for OLS Method

Rep.	Time (days)	Death	Dose (Concentration) 12.5	25	75	100
Model 1						
1, 2	1	Cumulative	1.018741	0.912659	0.763774	0.728472
		Estimate	1.018741	0.912659	0.763774	0.728472
	2	Cumulative	1.846860	1.682244	1.440435	1.381251
		Estimate	0.828119	0.769585	0.676662	0.652778
	3	Cumulative	2.698293	2.512333	2.219169	2.143833
		Estimate	0.851433	0.830089	0.778734	0.762582
	4	Cumulative	3.409524	3.258638	2.992711	2.919015
		Estimate	0.711232	0.746305	0.773541	0.775182
Model 2						
1, 2	1	Cumulative	1.015415	0.909625	0.761172	0.725977
		Estimate	1.015415	0.909625	0.761172	0.725977
	2	Cumulative	1.836739	1.672648	1.431769	1.372839
		Estimate	0.821324	0.763023	0.670597	0.646862
	3	Cumulative	2.681622	2.495560	2.202759	2.127608
		Estimate	0.844883	0.822912	0.770990	0.754770
	4	Cumulative	3.392235	3.239545	2.971537	2.897467
		Estimate	0.710613	0.743986	0.768778	0.769859
Model 3						
1, 2	1	Cumulative	1.018741	0.912659	0.763774	0.728472
		Estimate	1.018741	0.912659	0.763774	0.728472
	2	Cumulative	1.935649	1.766663	1.516964	1.455598
		Estimate	0.916909	0.854004	0.753191	0.727125
	3	Cumulative	2.849363	2.665547	2.370688	2.294012
		Estimate	0.913714	0.898884	0.853724	0.838415
	4	Cumulative	3.548790	3.415071	3.170255	3.100665
		Estimate	0.699427	0.749524	0.799567	0.806652
Model 4						
1, 2	1	Cumulative	1.580575	1.605830	1.646378	1.657101
		Estimate	1.580575	1.605830	1.646378	1.657101
	2	Cumulative	2.613282	2.643605	2.691556	2.704084
		Estimate	1.032707	1.037776	1.045178	1.046984
	3	Cumulative	3.413634	3.436668	3.472244	3.481367
		Estimate	0.800352	0.793062	0.780688	0.777283
	4	Cumulative	3.848304	3.858318	3.873225	3.876937
		Estimate	0.434669	0.421650	0.400981	0.395569
Model 5						
1, 2	1	Cumulative	0.407931	0.361676	0.298427	0.283703
		Estimate	0.407931	0.361676	0.298427	0.283703
	2	Cumulative	0.811194	0.724058	0.602907	0.574371
		Estimate	0.403263	0.362381	0.304479	0.290668
	3	Cumulative	1.347535	1.214705	1.025206	0.979759
		Estimate	0.536340	0.490648	0.422300	0.405389
	4	Cumulative	2.013813	1.841337	1.585098	1.521888
		Estimate	0.666278	0.626631	0.559891	0.542128
Model 6						
1, 2	1	Cumulative	1.015415	0.909625	0.761172	0.725977
		Estimate	1.015415	0.909625	0.761172	0.725977
	2	Cumulative	1.925285	1.756786	1.507984	1.446868
		Estimate	0.909870	0.847162	0.746812	0.720891

	3	Cumulative	2.832997	2.648838	2.354016	2.277454
		Estimate	0.907712	0.892051	0.846032	0.830586
	4	Cumulative	3.533690	3.397859	3.150331	3.080188
		Estimate	0.700693	0.749021	0.796315	0.802735
			Model 7			
1, 2	1	Cumulative	1.575957	1.601164	1.641639	1.652342
		Estimate	1.575957	1.601164	1.641639	1.652342
	2	Cumulative	2.602115	2.632453	2.680439	2.692978
		Estimate	1.026158	1.031289	1.038800	1.040636
	3	Cumulative	3.400732	3.424011	3.459987	3.469218
		Estimate	0.798617	0.791557	0.779548	0.776239
	4	Cumulative	3.840628	3.850995	3.866449	3.870301
		Estimate	0.439896	0.426984	0.406462	0.401084
			Model 8			
1, 2	1	Cumulative	0.406465	0.360368	0.297339	0.282666
		Estimate	0.406465	0.360368	0.297339	0.282666
	2	Cumulative	0.805718	0.719101	0.598702	0.570348
		Estimate	0.399253	0.358733	0.301363	0.287682
	3	Cumulative	1.335155	1.203255	1.015205	0.970125
		Estimate	0.529437	0.484154	0.416502	0.399777
	4	Cumulative	1.992726	1.821157	1.566644	1.503924
		Estimate	0.657572	0.617903	0.551440	0.533799
			Model 9			
1, 2	1	Cumulative	1.580575	1.605830	1.646378	1.657101
		Estimate	1.580575	1.605830	1.646378	1.657101
	2	Cumulative	2.709651	2.739763	2.787285	2.799682
		Estimate	1.129076	1.133933	1.140907	1.142582
	3	Cumulative	3.525174	3.545830	3.577552	3.585649
		Estimate	0.815523	0.806067	0.790266	0.785967
	4	Cumulative	3.904245	3.911420	3.921970	3.924570
		Estimate	0.379071	0.365590	0.344418	0.338921
			Model 10			
1, 2	1	Cumulative	0.407931	0.361676	0.298427	0.283703
		Estimate	0.407931	0.361676	0.298427	0.283703
	2	Cumulative	0.859958	0.768235	0.640433	0.610285
		Estimate	0.452027	0.406558	0.342006	0.326582
	3	Cumulative	1.464610	1.323310	1.120448	1.071580
		Estimate	0.604653	0.555075	0.480015	0.461296
	4	Cumulative	2.200008	2.020661	1.750509	1.683226
		Estimate	0.735398	0.697351	0.630061	0.611646
			Model 11			
1, 2	1	Cumulative	0.672187	0.684941	0.705597	0.711097
		Estimate	0.672187	0.684941	0.705597	0.711097
	2	Cumulative	1.285414	1.307288	1.342520	1.351859
		Estimate	0.613227	0.622347	0.636922	0.640762
	3	Cumulative	2.018883	2.047723	2.093776	2.105902
		Estimate	0.733470	0.740435	0.751256	0.754042
	4	Cumulative	2.792088	2.821900	2.868865	2.881099
		Estimate	0.773204	0.774177	0.775089	0.775198
			Model 12			
1, 2	1	Cumulative	1.575957	1.601164	1.641639	1.652342
		Estimate	1.575957	1.601164	1.641639	1.652342
	2	Cumulative	2.698551	2.728694	2.776278	2.788693
		Estimate	1.122593	1.127530	1.134639	1.136351

	3	Cumulative	3.513564	3.534491	3.566649	3.574862
		Estimate	0.815013	0.805797	0.790371	0.786169
	4	Cumulative	3.898699	3.906180	3.917195	3.919914
		Estimate	0.385135	0.371689	0.350546	0.345052
			Model 13			
1, 2	1	Cumulative	0.406465	0.360368	0.297339	0.282666
		Estimate	0.406465	0.360368	0.297339	0.282666
	2	Cumulative	0.854198	0.763012	0.635992	0.606033
		Estimate	0.447732	0.402644	0.338653	0.323368
	3	Cumulative	1.451473	1.311094	1.109700	1.061211
		Estimate	0.597275	0.548081	0.473708	0.455178
	4	Cumulative	2.178195	1.999543	1.730892	1.664061
		Estimate	0.726722	0.688449	0.621192	0.602850
			Model 14			
1, 2	1	Cumulative	0.669864	0.682578	0.703172	0.708655
		Estimate	0.669864	0.682578	0.703172	0.708655
	2	Cumulative	1.277435	1.299207	1.334279	1.343577
		Estimate	0.607570	0.616629	0.631108	0.634922
	3	Cumulative	2.003042	2.031785	2.077694	2.089783
		Estimate	0.725607	0.732577	0.743414	0.746206
	4	Cumulative	2.770071	2.799974	2.847106	2.859389
		Estimate	0.767029	0.768189	0.769413	0.769606
			Model 15			
1, 2	1	Cumulative	0.672187	0.684941	0.705597	0.711097
		Estimate	0.672187	0.684941	0.705597	0.711097
	2	Cumulative	1.356028	1.378775	1.415387	1.425087
		Estimate	0.683841	0.693835	0.709790	0.713990
	3	Cumulative	2.166090	2.195697	2.242874	2.255275
		Estimate	0.810062	0.816922	0.827487	0.830188
	4	Cumulative	2.979255	3.007940	3.052922	3.064597
		Estimate	0.813165	0.812243	0.810047	0.809321
			Model 16			
1, 2	1	Cumulative	0.669864	0.682578	0.703172	0.708655
		Estimate	0.669864	0.682578	0.703172	0.708655
	2	Cumulative	1.347727	1.370374	1.406827	1.416486
		Estimate	0.677863	0.687796	0.703656	0.707831
	3	Cumulative	2.149807	2.179341	2.226413	2.238789
		Estimate	0.802080	0.808967	0.819586	0.822303
	4	Cumulative	2.958007	2.986854	3.032114	3.043867
		Estimate	0.808200	0.807513	0.805701	0.805078
			Model 17			
1, 2	1	Cumulative	1.156191	1.176367	1.208905	1.217539
		Estimate	1.156191	1.176367	1.208905	1.217539
	2	Cumulative	3.036551	3.064754	3.108910	3.120356
		Estimate	1.880360	1.888387	1.900005	1.902817
	3	Cumulative	3.972285	3.975017	3.978900	3.979832
		Estimate	0.935734	0.910263	0.869990	0.859475
	4	Cumulative	3.999999	3.999999	3.999999	3.999999
		Estimate	0.027714	0.024983	0.021100	0.020168

			Model 18			
1, 2	1	Cumulative	0.669864	0.682578	0.703172	0.708655
		Estimate	0.669864	0.682578	0.703172	0.708655

	2	Cumulative	1.658078	1.684097	1.725837	1.736867
		Estimate	0.988214	1.001519	1.022666	1.028212
	3	Cumulative	2.761836	2.791772	2.838963	2.851262
		Estimate	1.103758	1.107674	1.113125	1.114395
	4	Cumulative	3.592248	3.611224	3.640244	3.647628
		Estimate	0.830411	0.819452	0.801281	0.796365
Model 19						
1, 2	1	Cumulative	1.156191	1.176367	1.208905	1.217540
		Estimate	1.156191	1.176367	1.208905	1.217540
	2	Cumulative	3.373990	3.397759	3.434537	3.443982
		Estimate	2.217799	2.221392	2.225631	2.226442
	3	Cumulative	3.997921	3.998225	3.998627	3.998718
		Estimate	0.623931	0.600466	0.564090	0.554736
	4	Cumulative	4.000000	4.000000	4.000000	4.000000
		Estimate	0.002079	0.001775	0.001373	0.001282

Table 9. The cumulative and estimated response rates for ML Method

Rep.	Time (days)	Death	Dose (Concentration)			
			12.5	25	75	100
Models 1,2,3,7						
1, 2	1	Cumulative	0.652535	0.416912	0.200175	0.164694
		Estimate	0.652535	0.416912	0.200175	0.164694
	2	Cumulative	2.157267	1.522434	0.800904	0.668858
		Estimate	1.504733	1.105522	0.600730	0.504164
	3	Cumulative	3.513791	2.912584	1.821188	1.567891
		Estimate	1.356524	1.390149	1.020284	0.899033
	4	Cumulative	3.964571	3.784533	2.975964	2.689493
		Estimate	0.450780	0.871950	1.154776	1.121602
Models 4,8,10,13						
1, 2	1	Cumulative	4.000000	4.000000	4.000000	4.000000
		Estimate	4.000000	4.000000	4.000000	4.000000
	2	Cumulative	4.000000	4.000000	4.000000	4.000000
		Estimate	0.000000	0.000000	0.000000	0.000000
	3	Cumulative	4.000000	4.000000	4.000000	4.000000
		Estimate	0.000000	0.000000	0.000000	0.000000
	4	Cumulative	4.000000	4.000000	4.000000	4.000000
		Estimate	0.000000	0.000000	0.000000	0.000000
Models 5,9,11,14						
1, 2	1	Cumulative	0.000002	0.000001	0.000001	0.000000
		Estimate	0.000002	0.000001	0.000001	0.000000
	2	Cumulative	0.000008	0.000005	0.000002	0.000002
		Estimate	0.000006	0.000004	0.000002	0.000001
	3	Cumulative	0.000021	0.000013	0.000006	0.000005
		Estimate	0.000013	0.000008	0.000004	0.000003
	4	Cumulative	0.000047	0.000029	0.000014	0.000011
		Estimate	0.000026	0.000016	0.000008	0.000006
Models 6,12,15,16						
1, 2	1	Cumulative	0.005464	0.030485	0.442526	0.852252
		Estimate	0.005464	0.030485	0.442526	0.852252
	2	Cumulative	0.023726	0.130984	1.598594	2.590079

		Estimate	0.018262	0.100499	1.156067	1.737827
	3	Cumulative	0.064185	0.346210	3.001090	3.765209
		Estimate	0.040459	0.215226	1.402496	1.175130
	4	Cumulative	0.142521	0.735019	3.821890	3.993077
		Estimate	0.078336	0.388809	0.820800	0.227868
Model 17						
1, 2	1	Cumulative	0.010593	0.058923	0.813696	1.486949
		Estimate	0.010593	0.058923	0.813696	1.486949
	2	Cumulative	0.088551	0.471013	3.413573	3.920940
		Estimate	0.077958	0.412090	2.599877	2.433991
	3	Cumulative	0.445495	1.934278	3.999000	4.000000
		Estimate	0.356944	1.463266	0.586268	0.079060
	4	Cumulative	1.606939	3.774333	4.000000	4.000000
		Estimate	1.161445	1.840055	0.000160	4.11E-09
Model 18						
1, 2	1	Cumulative	0.005464	0.030485	0.442526	0.852252
		Estimate	0.005464	0.030485	0.442526	0.852252
	2	Cumulative	0.015295	0.084851	1.120239	1.956280
		Estimate	0.009831	0.054366	0.677713	1.104028
	3	Cumulative	0.032083	0.176269	1.995046	3.024897
		Estimate	0.016787	0.091418	0.874807	1.068617
	4	Cumulative	0.059734	0.323026	2.899416	3.713771
		Estimate	0.027652	0.146758	0.904370	0.688874
Model 19						
1, 2	1	Cumulative	0.010593	0.058923	0.813696	1.486949
		Estimate	0.010593	0.058923	0.813696	1.486949
	2	Cumulative	0.057252	0.310047	2.838349	3.680374
		Estimate	0.046659	0.251124	2.024654	2.193425
	3	Cumulative	0.228352	1.121340	3.974145	3.999866
		Estimate	0.171099	0.811292	1.135795	0.319492
	4	Cumulative	0.767534	2.785921	4.000000	4.000000
		Estimate	0.539182	1.664581	0.025855	0.000134

Table 8 shows that, in relation to the OLS method, all models provided cumulative values for response rates of breast cancer cells treated physically and environmentally that were less than 4, with the exception of model 19, which produced values that were equal to 4.

Related to the ML method, **Table 9** shows that six models (4,8,10,13,17, and 19) produced cumulative values equal to 4, whereas other models produced cumulative values below 4.

Now, the values of MSE for each model can be determined by using the formula (20) with the observed values for response rates in **Tables 2** and **3** and estimated values in **Tables 8** and **9**. The results according to each estimating method are given in Table 10, where the bold numbers represent the associated values of the best model.

Table 10. The MSE value with the OLS and ML methods

Model	OLS method		ML method	
	Physical Treatment	Green Treatment	Physical Treatment	Green Treatment
1	0.111641	0.064690	0.396101	0.303643
2	0.106413	0.062718	0.380257	0.291497
3	0.115889	0.058925	0.380257	0.291497
4	0.390278	0.310393	3.978605	3.936748
5	0.204173	0.255596	0.701694	0.888094
6	0.110147	0.056561	0.231475	0.333524
7	0.370256	0.293933	0.365632	0.280286
8	0.198639	0.249542	3.825582	3.785335
9	0.410069	0.328924	0.674705	0.853936
10	0.178690	0.214900	3.825582	3.785335
11	0.061955	0.046661	0.674705	0.853936
12	0.389466	0.311650	0.249280	0.359180
13	0.173773	0.210110	3.683894	3.645137
14	0.059495	0.046282	0.649716	0.822309
15	0.064128	0.036096	0.240048	0.345877
16	0.061036	**0.035413**	0.240048	0.345877
17	0.644657	0.556320	0.797178	0.764556
18	0.130385	0.063516	**0.151080**	0.270285
19	0.860582	0.774939	0.488225	0.507734

For the OLS method, **Table 10** demonstrates that the MSE values for the green treatment are lower than those for the physical treatment with all models except four models, which are 5, 8, 10, and 13. The same holds for the MSE values related to the ML method for nine models which are 1, 2, 3, 4, 7, 8, 10, 13, and 17. Further, it shows that the MSE values of OLS with all models except 7, 12, and 19 (physical treatment) and 7 and 19 (green treatment) are lower than those of the ML. For the OLS method related to the green treatment, model 16 is the best model with a value of MSE equal to 0.035413, and model 18 is the best for the ML method related to the physical treatment with a value of MSE equal to 0.151080. The best models indicate that the experiment's replications are not important. Generally, in comparing the MSE values for the best model related to OLS and ML methods, model 16 has the lowest MSE value. This indicates that the OLS method with green treatment has outperformed the ML method with physical treatment in providing the best model for the breast cancer experiment. Further, the estimates of the LD_{50} for the best model are then determined using the formula (21), the results are shown in **Table 11**.

Table 11. The estimates of the LD_{50} for the best model

Days	Model 16	Model 18
	OLS (Green Treatment)	ML (Physical Treatment)
1	3.04E+20	153.3492
2	5.23E+08	101.2839
3	0.351173	75.10801
4	2.72E-09	58.40109

According to **Table 11**, the LD_{50} estimates of the green and physical treatments related to OLS and ML methods exhibit a decreasing dose-time relationship over four days.

7. Conclusion

For the relationship of response with dose and time, nineteen models are constructed based on the MW model. The unknown parameters are estimated using the OLS and ML estimation methods. The real experiment is focused on using real data to cure breast cancer by employing the therapeutic zinc selenide, which was physically created using plasma and environmentally using plant extract. The cumulative and estimated response rates are computed for each model. With the lowest MSE, the best models are determined, and then the estimated LD_{50} is introduced. Models 16 and 18 (where the experiment's replications are not important) represent respectively the best model with the OLS and ML estimation methods, and over four days, the LD_{50} estimates related to the OLS and ML methods exhibit a decreasing dose-time relationship. Finally, in providing the best model for the breast cancer experiment, the OLS method has outperformed the ML method.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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