

DISTRIBUTION OF SEVERAL INTERNAL DOSE METRICS AT VARYING LEVELS OF DCM

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1. INTRODUCTION

Pharmacokinetics(PK) is the branch of pharmacology that deals with the fate and transport of a drug or other substance within an organism. This branch of pharmacology focuses on what the body does to a substance in its system. PK accounts for absorption, distribution, metabolism, and excretion(ADME) of the substance. [3] In this application, we are focused on physiologically based PK (PBPK) models. A PBPK model might be considered a chemical engineering representation of a biological organism. The model parameters are based on anatomy, physiology, and biochemical properties. A PBPK model is used for various types of extrapolations: between species, between exposure routes, between exposure scenarios, and within a species. [3]

In this research, we completed extrapolations between routes and species. The routes by which rats were exposed during toxicological studies were oral doses (occurring as discrete events) and inhalation exposures (occurring as semi-continuous events). [3] The aim was to find a dosage that would provide a specific internal dose metric whether the dose was given orally or by inhalation, occurring discretely or semi-continuously. There was also a PBPK model that extrapolated data from rats to humans. [3] The distribution of the human PK of the substance was studied to determine when the majority of the population would experience an adverse effect to the substance.

The substance that was being studied in this research was Dichloromethane (DCM, methylene chloride). DCM is an industrial solvent that has many uses such as paint stripping and decaffeinating coffee. [4] DCM has potential for carcinogenic activity when inhaled which can result in tumors in the lungs and/or liver. [1] Since 1987, the United State Environmental Protection Agency (USEPA) has recognized the scientific value of using PBPK models to study carcinogens and have linked variability with overall model uncertainty by use of the Monte Carlo techniques. [5] The effects of DCM can be observed by exposing rats to DCM through inhalation then the effects can be extrapolated to humans through the PBPK models. [5]

The aim of this research is to obtain a parametric distribution fit of the empirical distribution of the interval dose metric in a simulated human population after exposure to DCM. There are four dose metric that are being analyzed: DM1L, DM2L, DM2LU, AVGCV. Parametric distribution types will be selected that best fit the empirical distributions. These distribution fits can be used to evaluate the effects of DCM on human populations.

Model Variables	Internal Dose Metrics
AM1L	DM1L: Metabolism via MFO pathway in liver per unit of liver volume
AM2L	DM2L: Metabolism via GST pathway in liver per unit of liver volume
AM2LU	DM2LU: Metabolism via GST pathway in lung per unit of lung volume
AUCV	AVGCV: Average venous blood concentration

2. METHODS

2.1. Rat Route-to-Route Extrapolation. To start, we conducted a route-to-route extrapolation for rats. Oral doses were given in a discrete manner. This discrete case gave rats an administered dose of DCM at 0800, 1200, and 1600 hours. The dose was 5mg/kg. The first aim was to find a continuous inhalation concentration that yielded the same internal dose as the discrete oral dosage. The inhalation concentration was changed manually until we found an average blood concentration in mg/L that matched both the discrete and continuous cases. Once this dose metric was obtained the same techniques could be applied to a rat to human extrapolation.

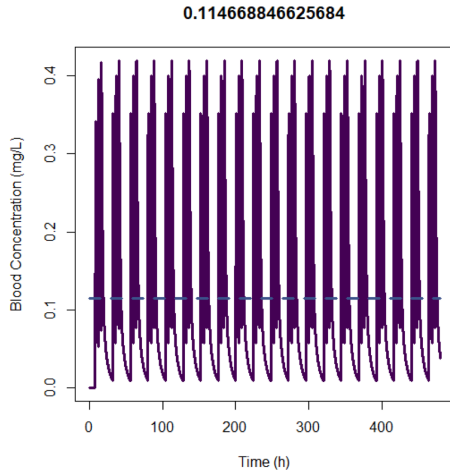


FIGURE 1. The routes by which rats were exposed during toxicological studies were oral doses (occurring as discrete events). Notice above the graph is the value of the dose metric (which is the dashed line) and it is close to the value of the other case.

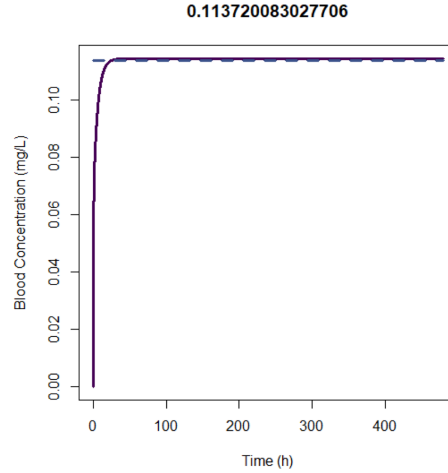


FIGURE 2. The routes by which rats were exposed during toxicological studies were inhalation exposures (occurring as semi-continuous events). Notice above the graph is the value of the dose metric (which is the dashed line) and it is close to the value of the other case.

2.2. Distribution of Internal Dose Metrics. In order to model the distribution of internal dose metrics, we used R studio with the function `set.seed(10579)` along with a DCM model and MCSim script provided by the Environmental Protection Agency (EPA). The parameter values we used were chosen via David et al. [1] with slight volume modifications from the EPA's IRIS

Toxicological Review [2]. It is important to note that the distribution from which the KFC (First-order metabolic rate constant for GST pathway) value was drawn only takes into account the +/- genotype for the GST-T1 polymorphism at the moment. We referred to Sweeny et al. and decided upon the concentrations 50 100 200 for testing our model.

2.2.1. State Variables. We began by setting several state variables that could be manipulated in various iterations of the R code. The *reps* parameter value specifies the number of repetitions or observations that will be run through the model; we set the reps amount to 100, 1000 and 5000. The days and times variables specify the number of days the model runs through and the time intervals when the output values from the model are collected; we set the days value to 14 and the times variable to collect every hour for all 24 hours in a day. The concentration value is the initial amount of the substance given to the individual at time 0. This number is changed during our testing process to 50, 100, or 200 [5]. The *set.seed* sets the randomization seed so that randomly generated values are recoverable through different iterations. Finally the metrics and tests are two lists of the variables used for calculating dose metrics and the names of the dose metrics that will be calculated. In our case we looked at the following model variables to calculate their respective internal dose metrics.

2.2.2. Prior to running the Model. We then move into the body of the code where we source the MCSim script to compile and load the model. Next, we set up the input parameters table of size according to the value of reps and define each of them as a random number following the truncated distributions [1] using the EnvStats library in R.

2.2.3. Running the Model. The next part of the code is a for loop which loops according to the number of reps input; it starts by randomly generating age and then generating a gender, vfm, and vlm according to the EPA toxicology review [2]. It then assigns values from the randomly created table to each of the input parameters, while making modifications to fractional body volumes to ensure that reasonable values are used to describe and individual (i.e. counter example). The code then sets our exposure concentration according to the concentration defined in the state variables. We then move to running the model according to the times, concentration, and parameters we have defined and set it to a temporary variable. Next, we define the last week of the model output values, which are the values that we will be analyzing, and create an array to hold this data. We do this inside of the for loop because the model results are stored in a data frame with specific variables that we apply to the array we created. Subsequently, we calculate the dose metrics of interest over the last week using the output parameters of interest and store it in a data frame. We use the formulas shown below for the calculation of the internal dose metrics where final values are the last values in the results, LW values are the results at the beginning of the last week and VL measures the volume of liver tissue. Finally we return to the top of the for loop and begin the next iteration.

$$\begin{aligned}
DM1L &= \frac{AM1L_{Final} - AM1L_{LW}}{7 * VL} \\
DM2L &= \frac{AM2L_{Final} - AM2L_{LW}}{7 * VL} \\
DM2LU &= \frac{AM2LU_{Final} - AM2LU_{LW}}{7 * VL} \\
AVGCV &= \frac{AUCV_{Final} - AUCV_{LW}}{7}
\end{aligned}$$

FIGURE 3. Formulas for Calculating Internal Dose Metrics

2.2.4. Plotting Results. Finally, we create 8 different 4 panel plots, 2 of each of the initial 4 internal dose metrics, using the `fitdistrplus` library in R, one where a lognormal distribution is fit and the other where a weibull distribution is fit. Each of these plots gives a historgam with fitted distribution, a Q-Q plot, a CDF, and a P-P plot. Prior to creating these plots, we use a standard interquartile range method to exclude outliers by removing any values that exceed 1.5 times the interquartile range. Along with each plot we give the parameter estimates and the AIC value for comparison of the 2 fits. Once we have the 8 different plots we cycle through the process again while changing the values for the “reps” and concentration parameters.

3. RESULTS

A total of 72 different 4 panel plots Figures 4-27 represent the results from a 50mg/kg concentration of AVGCV,DM1L,DM2L,DM2LU with 6 each dose metric in that order. Figures 28-51 represent the results from a 100mg/kg concentration of AVGCV,DM1L,DM2L,DM2LU with 6 each dose metric in that order. Figures 52-75 represent the results from a 200mg/kg concentration of AVGCV,DM1L,DM2L,DM2LU with 6 each dose metric in that order.

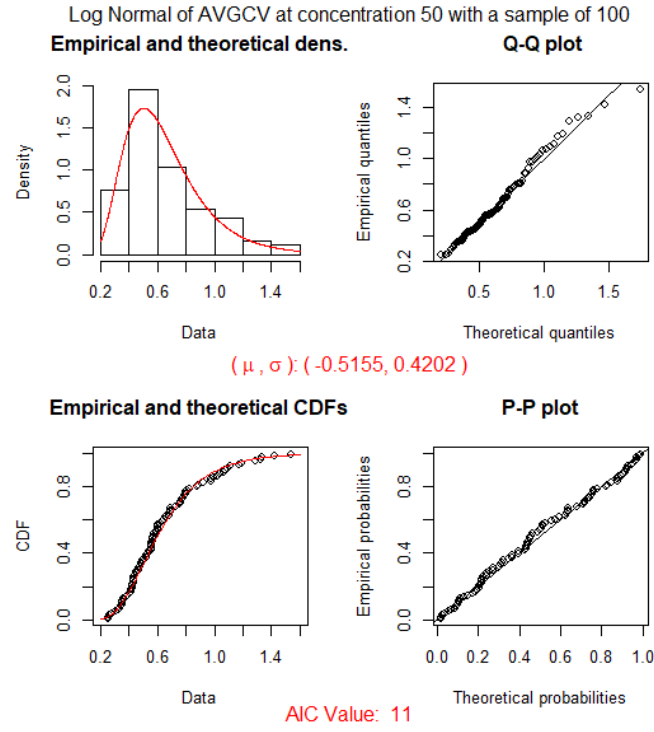


FIGURE 4. The AVGCV at concentration 50 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

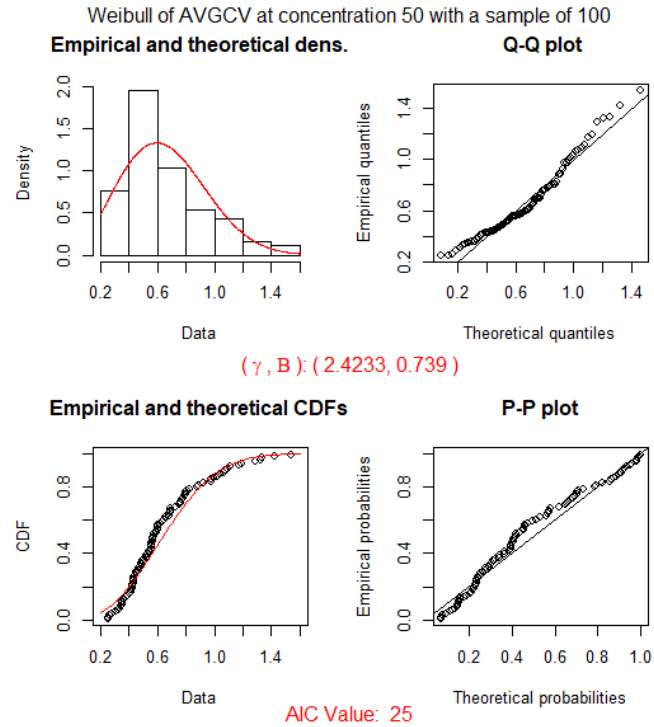


FIGURE 5. The AVGCV at concentration 50 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

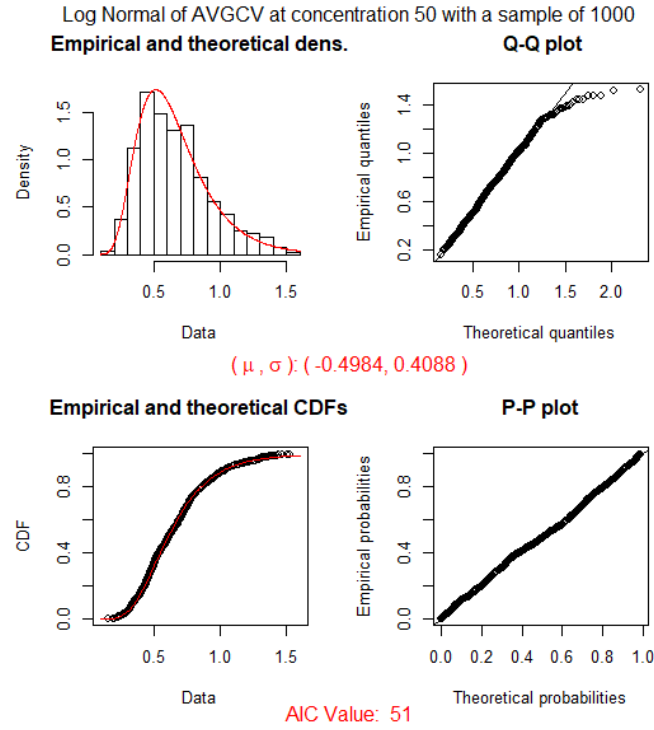


FIGURE 6. The AVGCV at concentration 50 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

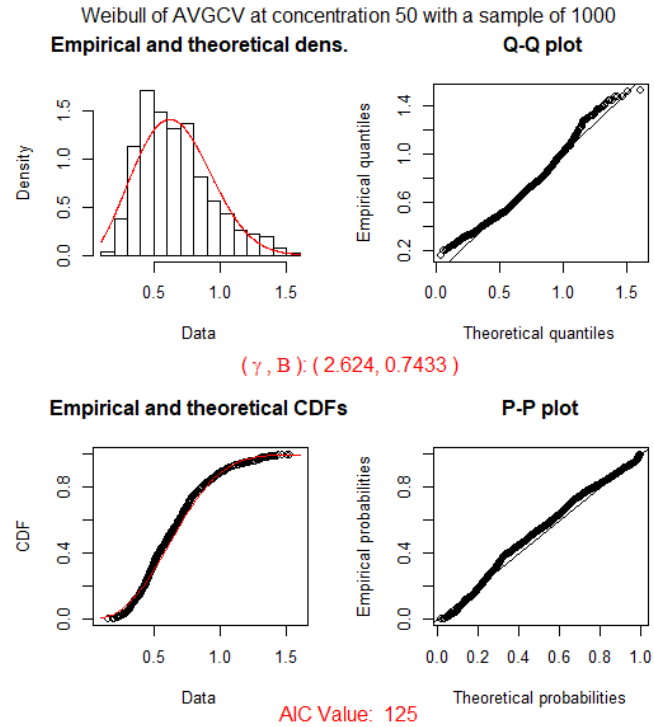


FIGURE 7. The AVGCV at concentration 50 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

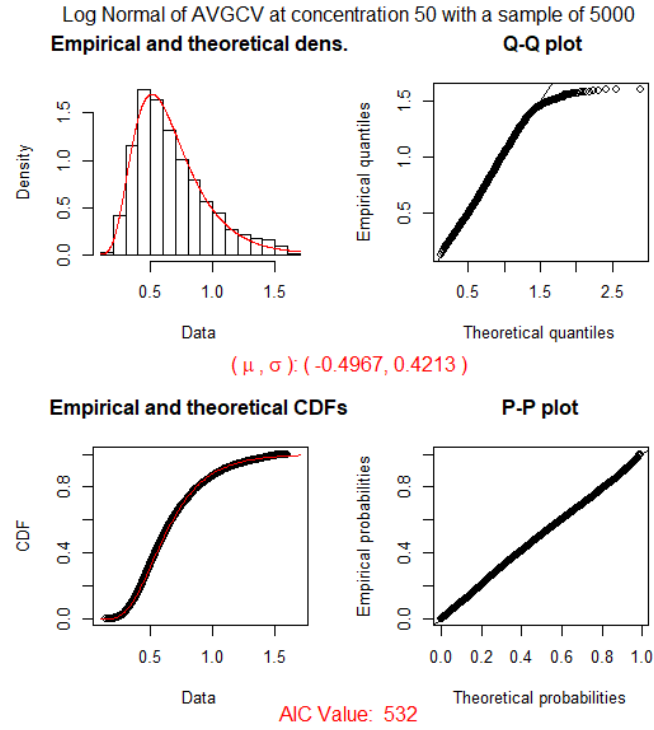


FIGURE 8. The AVGCV at concentration 50 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

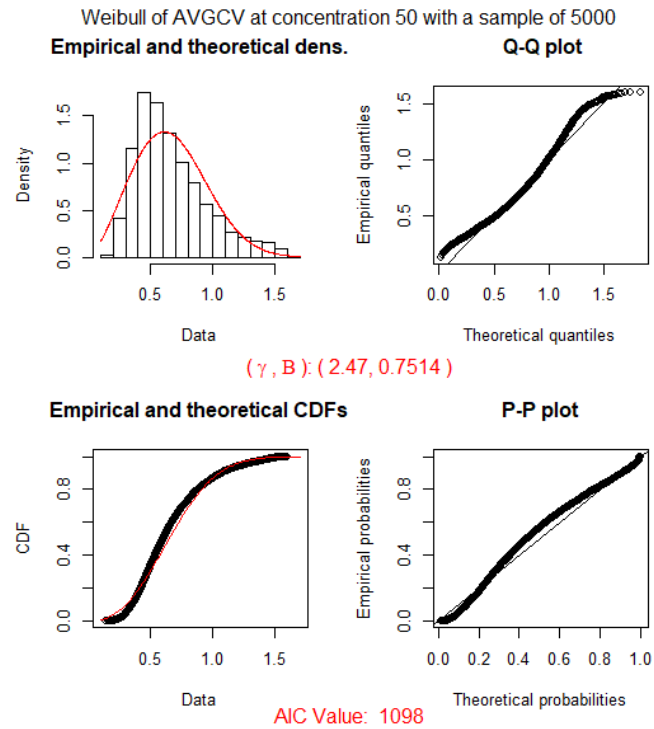


FIGURE 9. The AVGCV at concentration 50 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

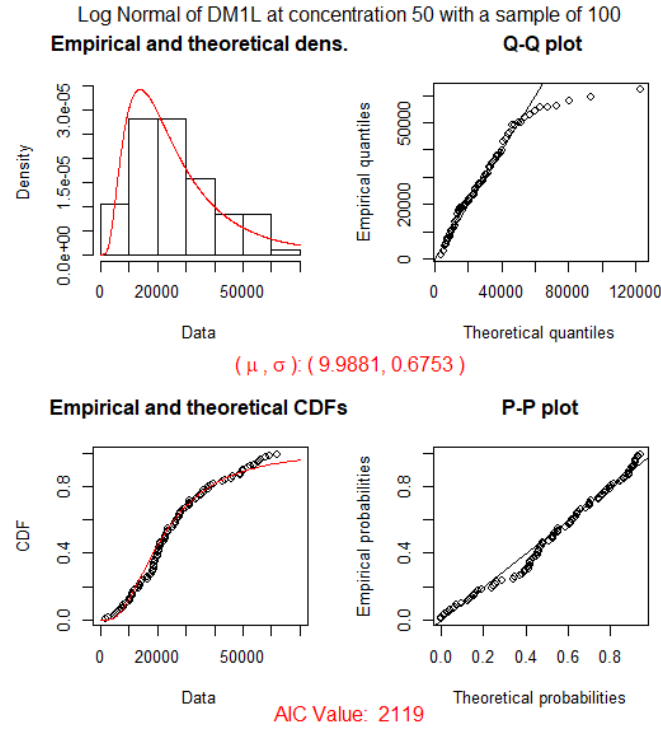


FIGURE 10. The DM1L at concentration 50 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

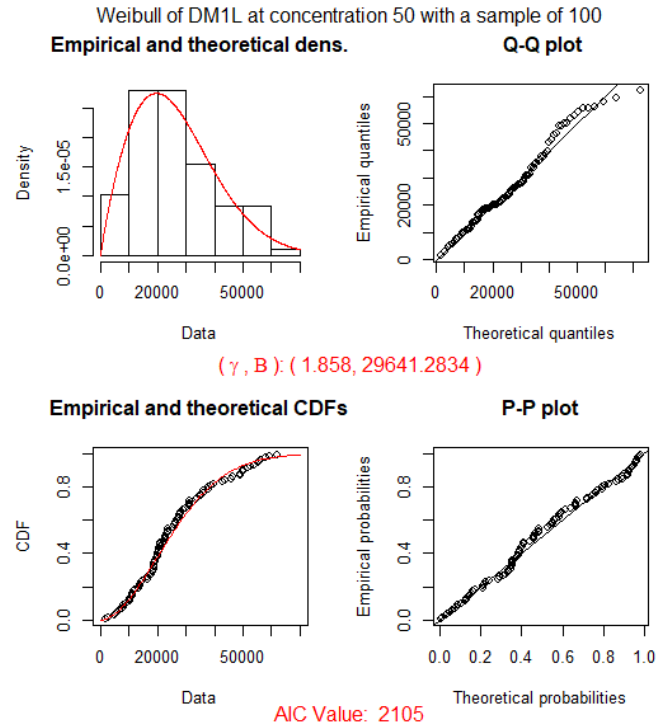


FIGURE 11. The DM1L at concentration 50 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

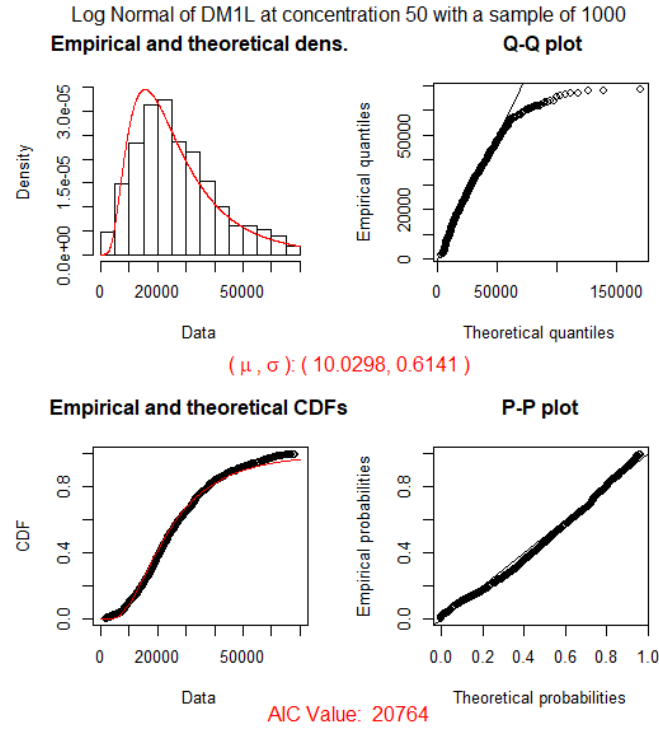


FIGURE 12. The DM1L at concentration 50 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

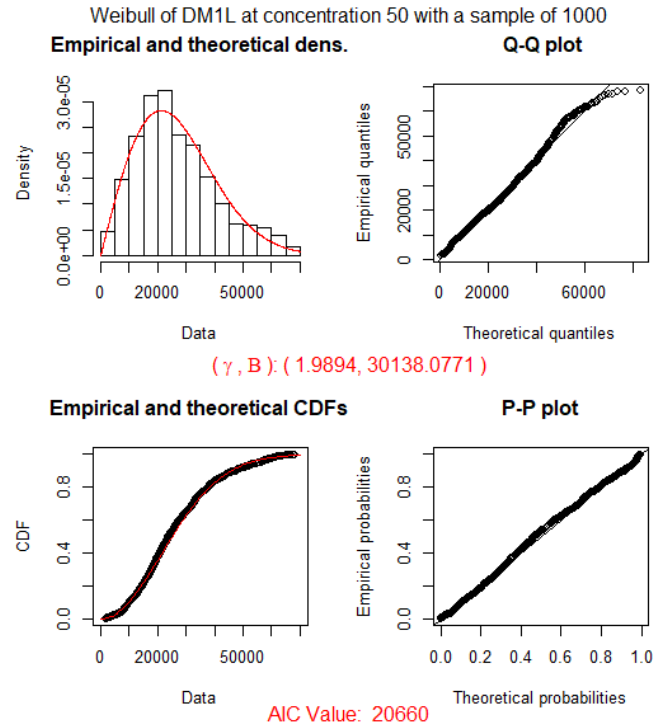


FIGURE 13. The DM1L at concentration 50 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

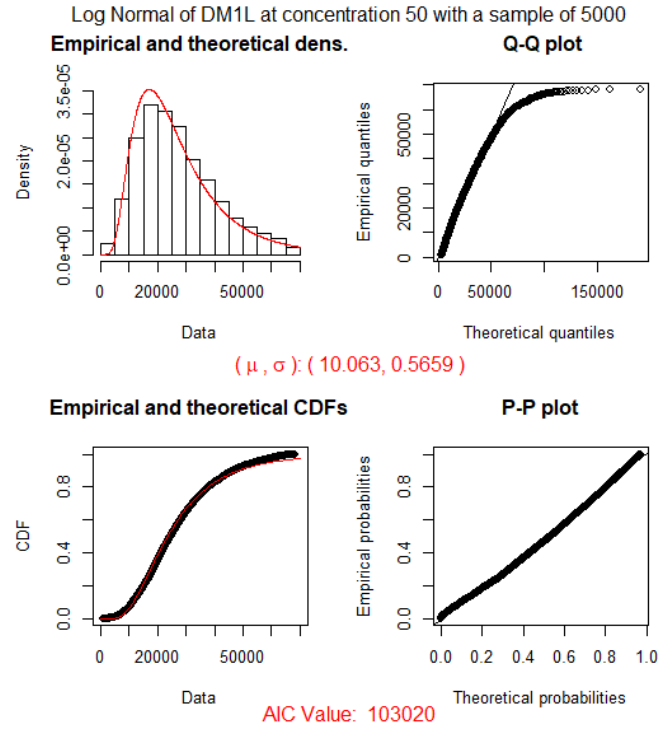


FIGURE 14. The DM1L at concentration 50 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

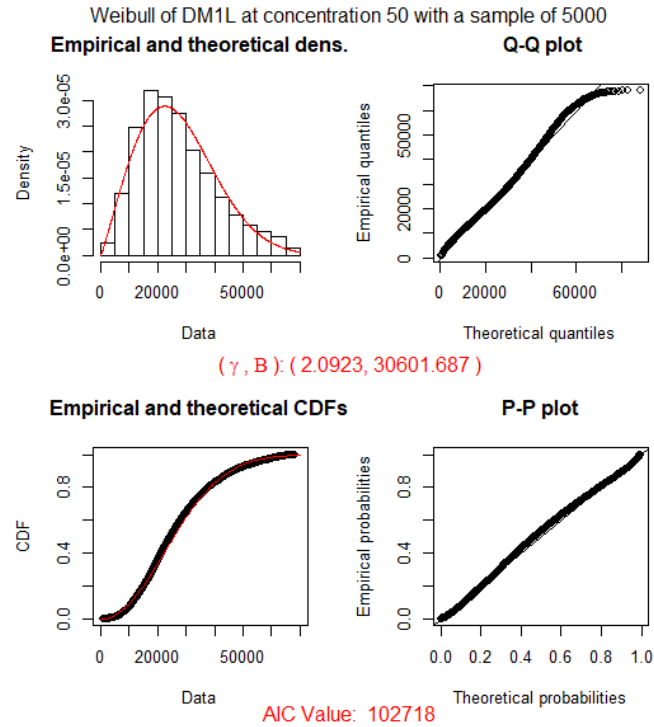


FIGURE 15. The DM1L at concentration 50 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

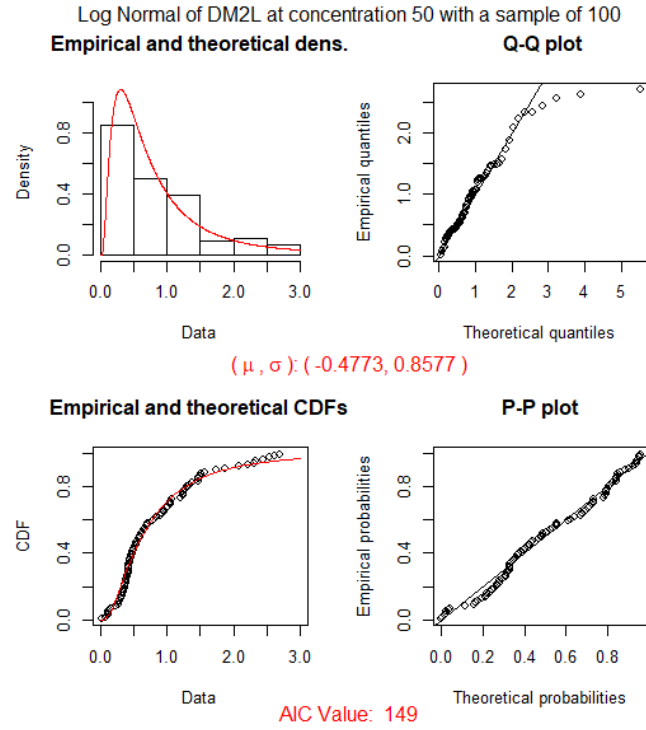


FIGURE 16. The DM2L at concentration 50 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

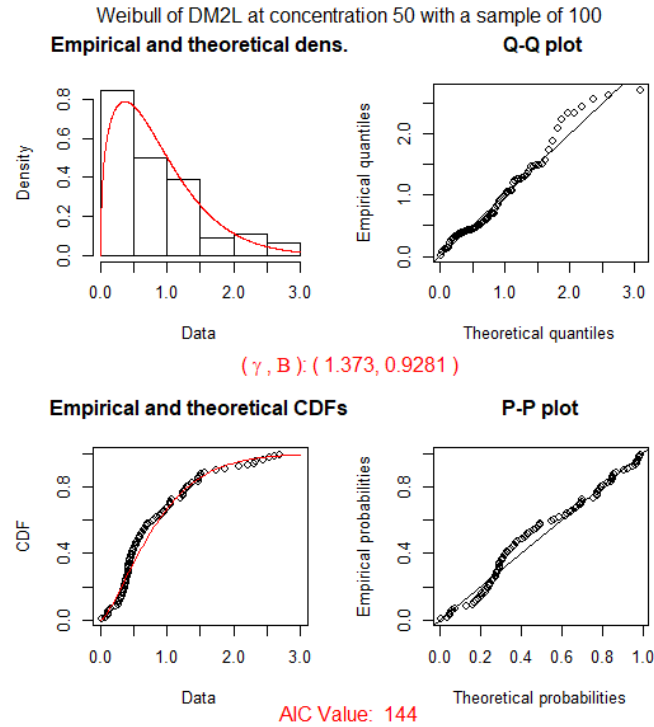


FIGURE 17. The DM2L at concentration 50 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

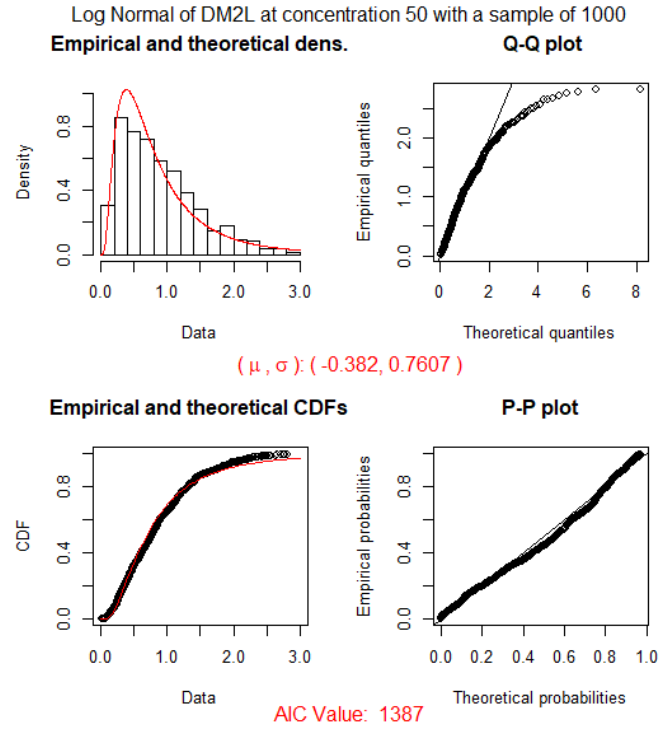


FIGURE 18. The DM2L at concentration 50 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

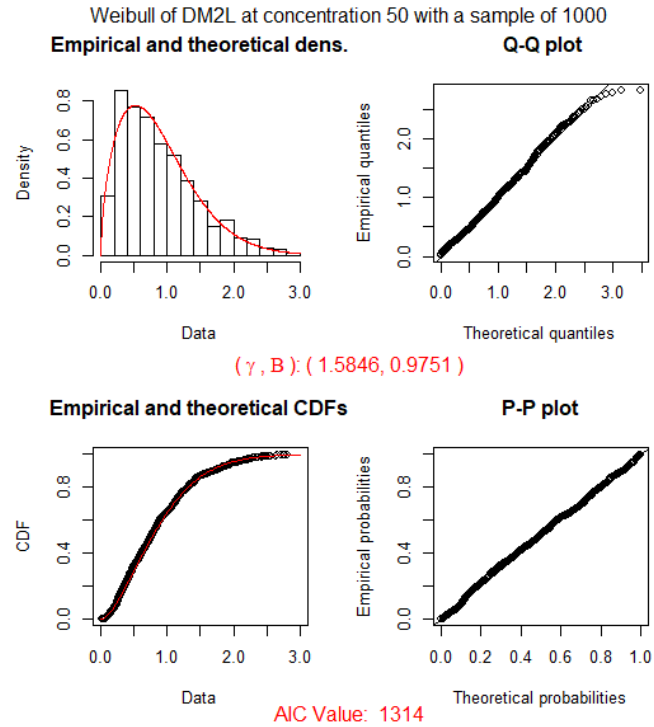


FIGURE 19. The DM2L at concentration 50 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

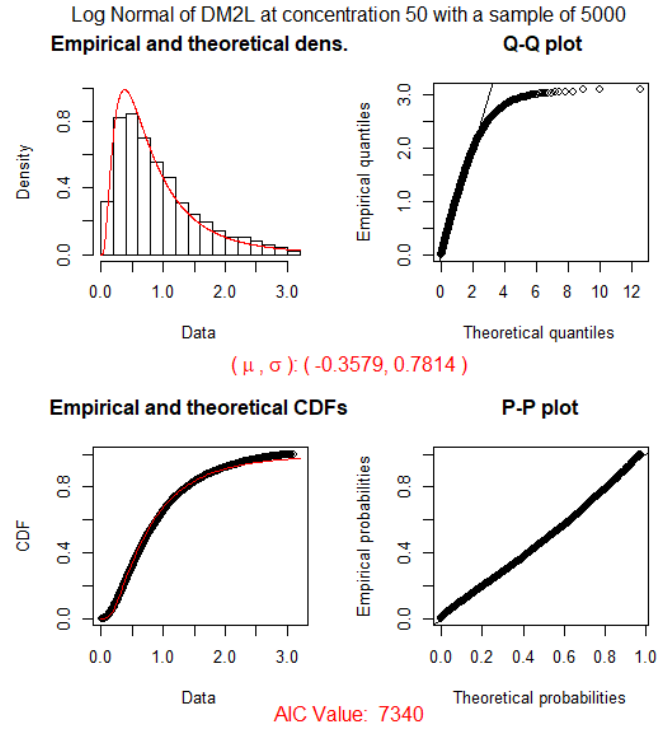


FIGURE 20. The DM2L at concentration 50 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

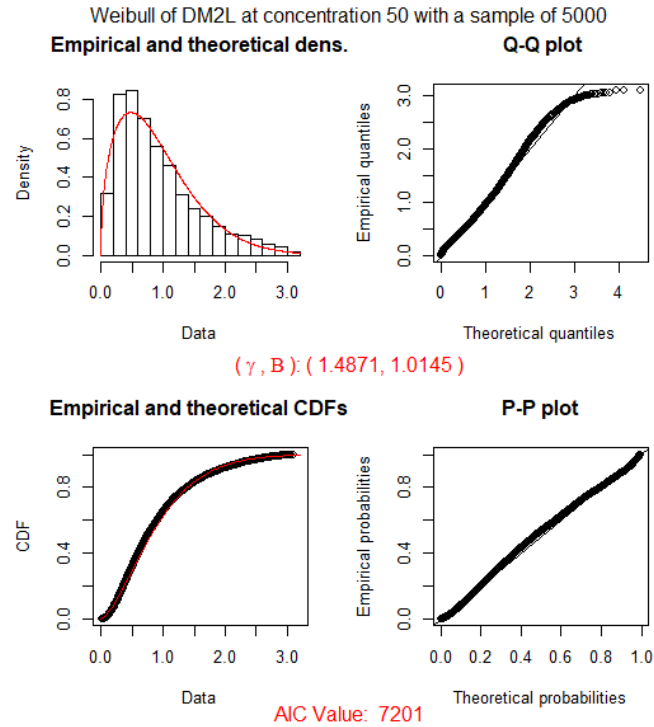


FIGURE 21. The DM2L at concentration 50 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

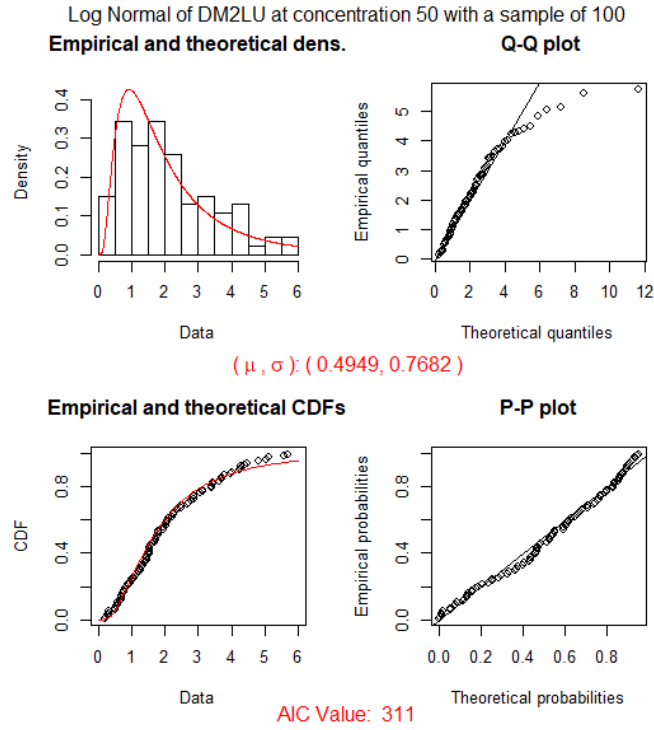


FIGURE 22. The DM2LU at concentration 50 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

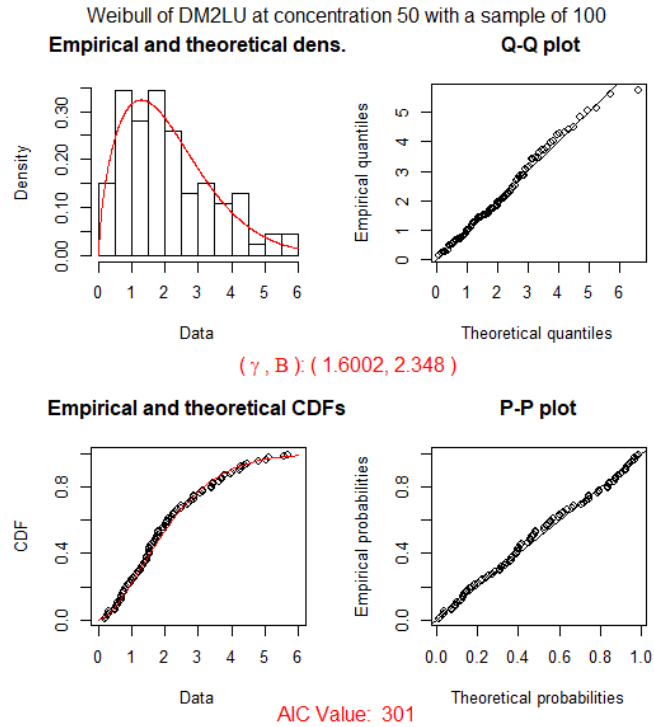


FIGURE 23. The DM2LU at concentration 50 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

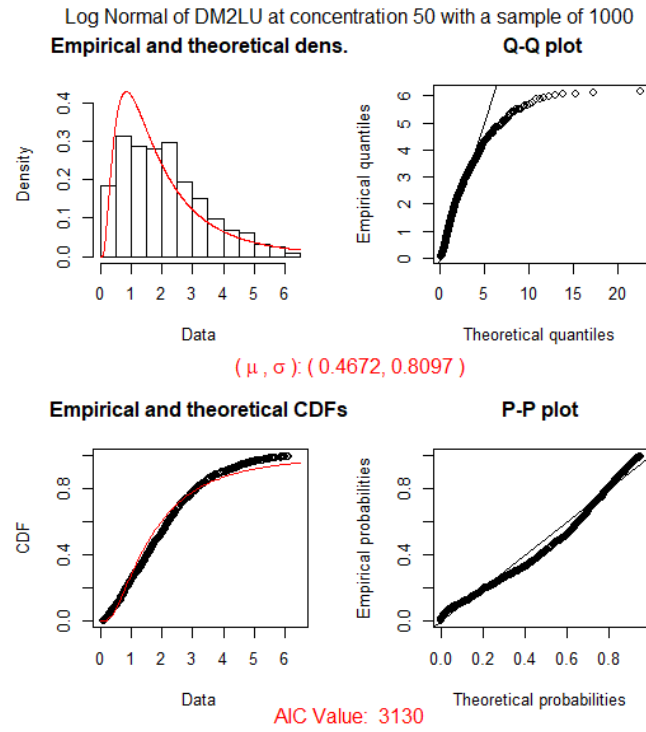


FIGURE 24. The DM2LU at concentration 50 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

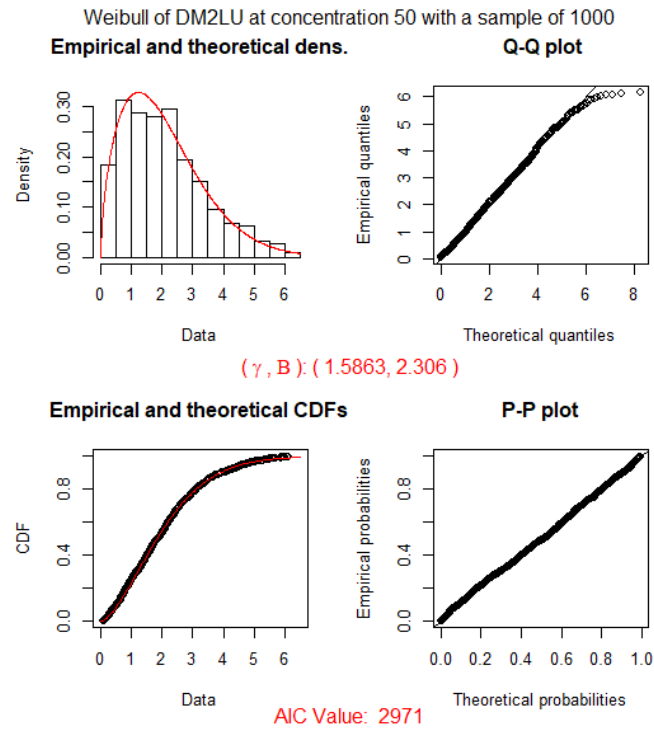


FIGURE 25. The DM2LU at concentration 50 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

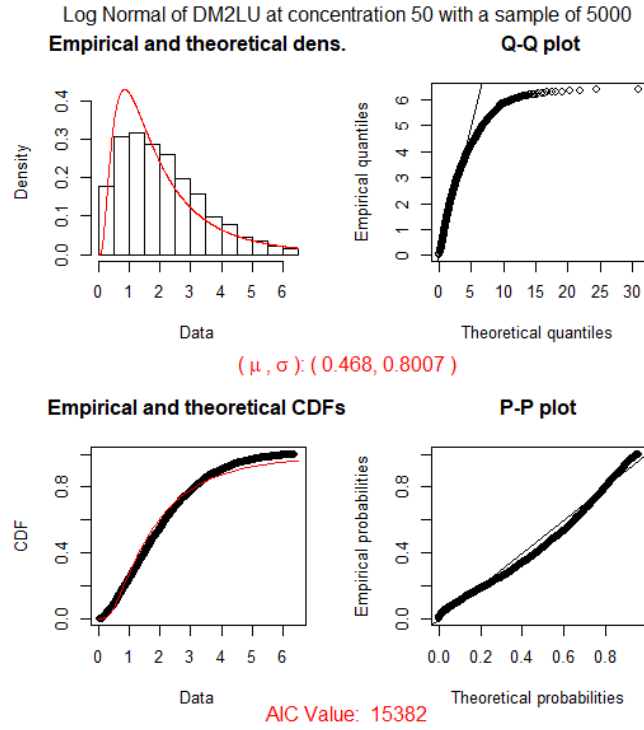


FIGURE 26. The DM2LU at concentration 50 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

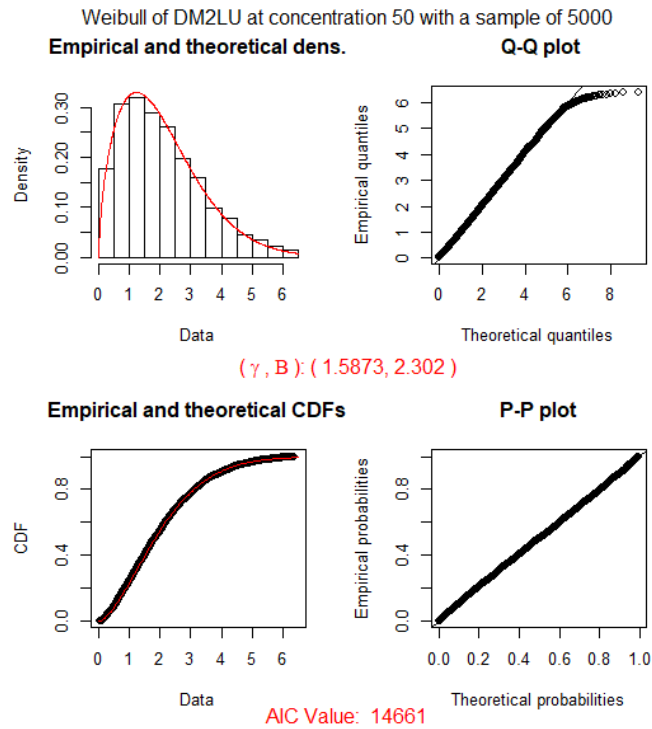


FIGURE 27. The DM2LU at concentration 50 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

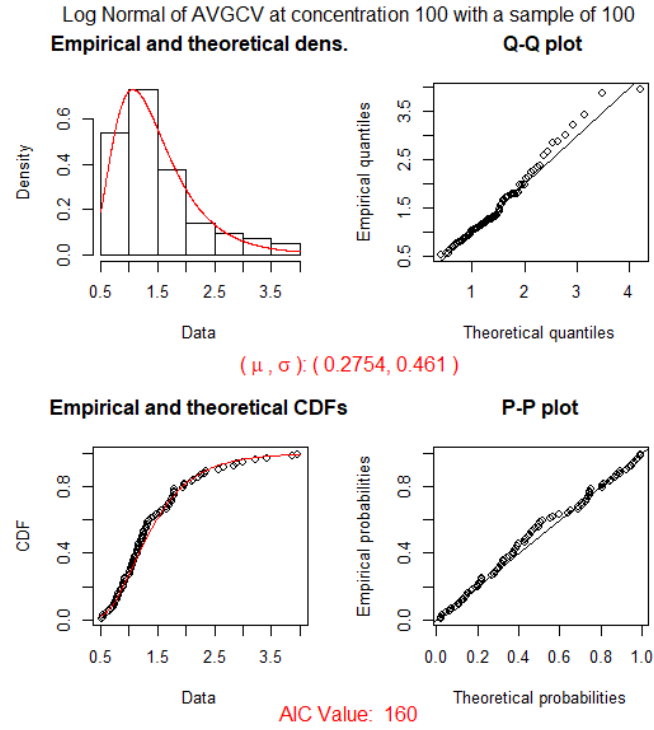


FIGURE 28. The AVGCV at concentration 100 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

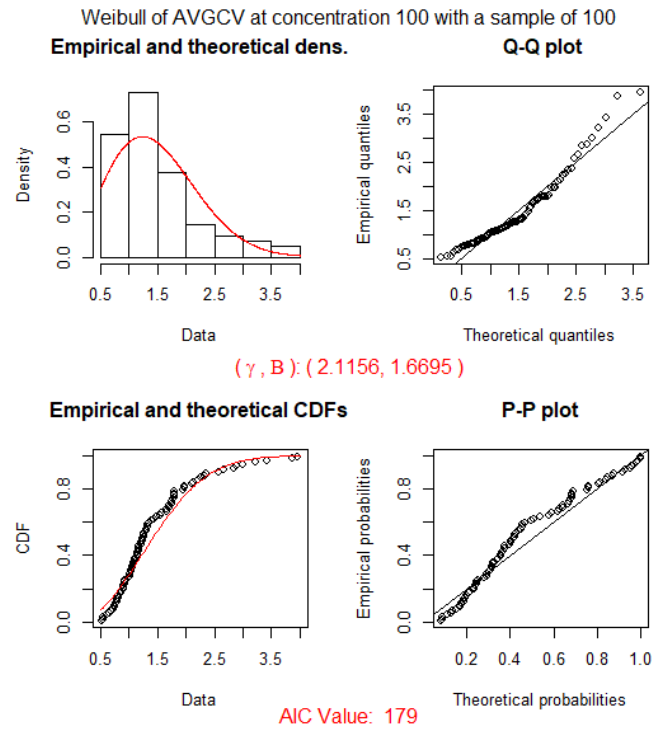


FIGURE 29. The AVGCV at concentration 100 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

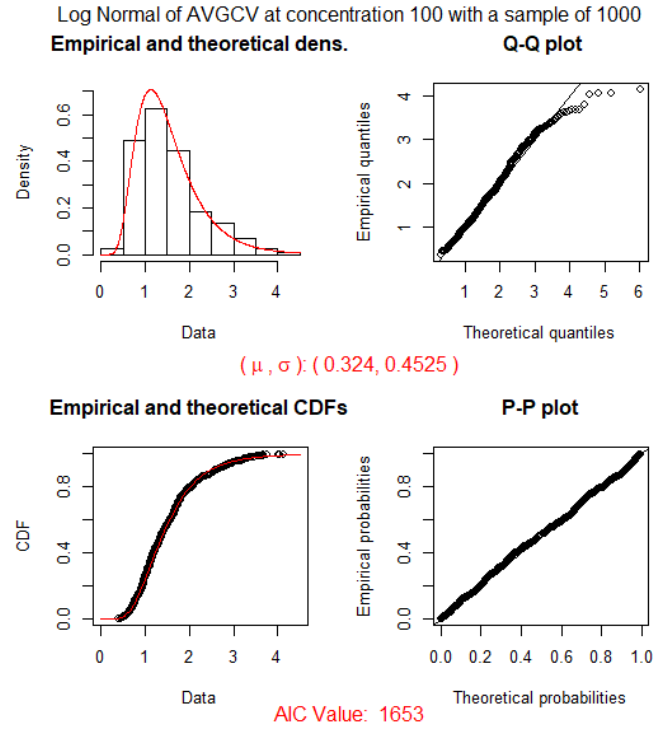


FIGURE 30. The AVGCV at concentration 100 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

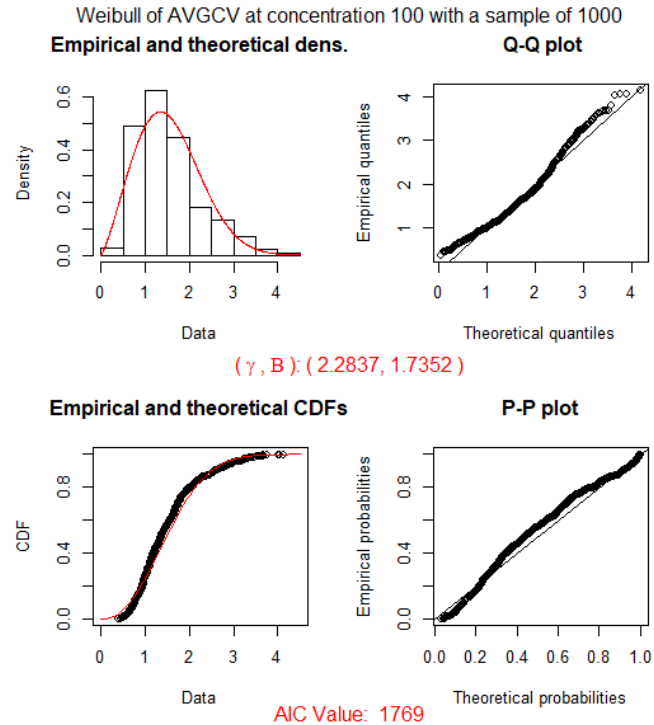


FIGURE 31. The AVGCV at concentration 100 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

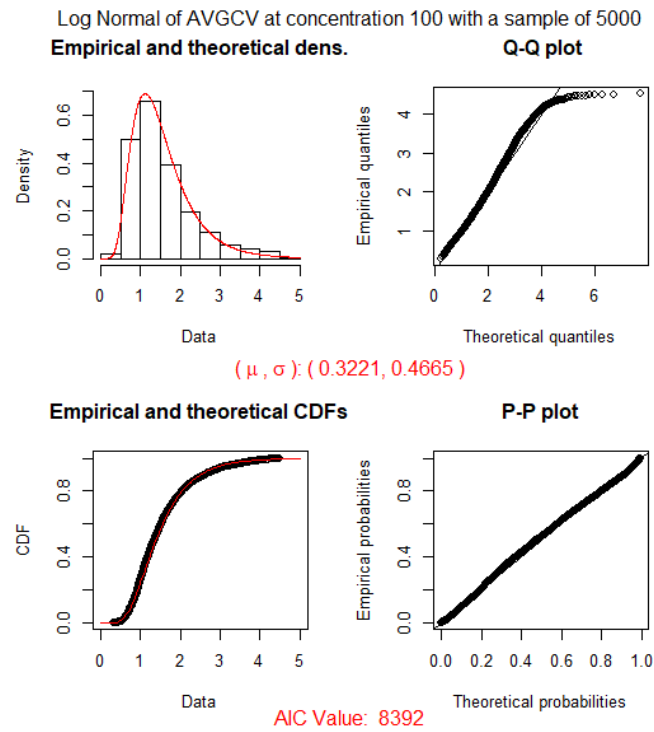


FIGURE 32. The AVGCV at concentration 100 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

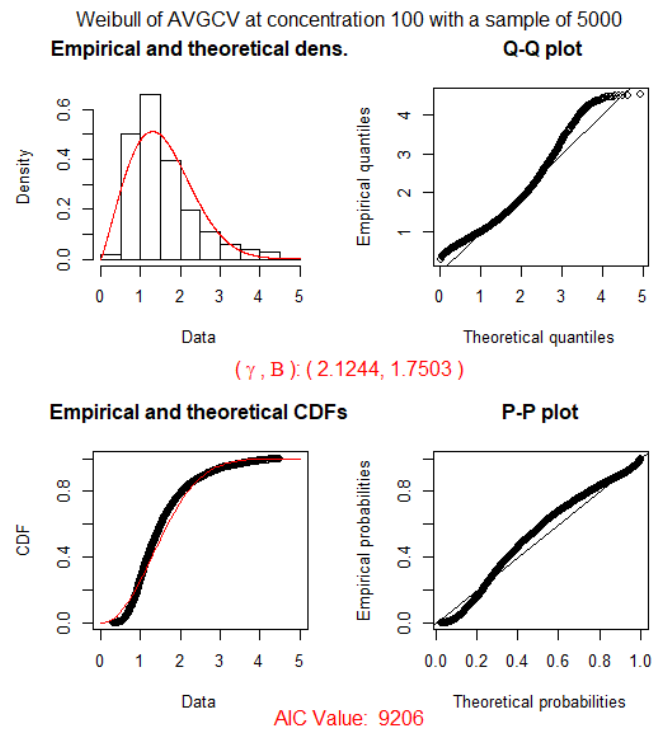


FIGURE 33. The AVGCV at concentration 100 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

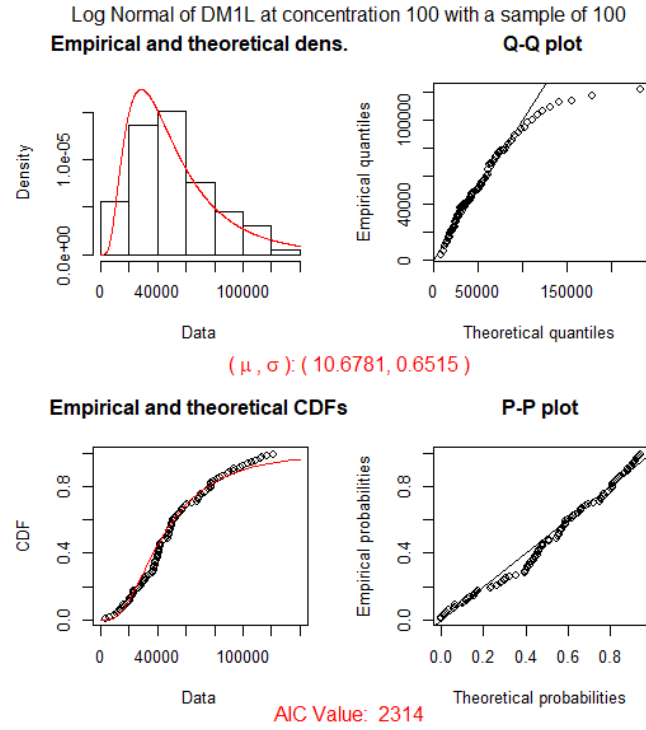


FIGURE 34. The DM1L at concentration 100 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

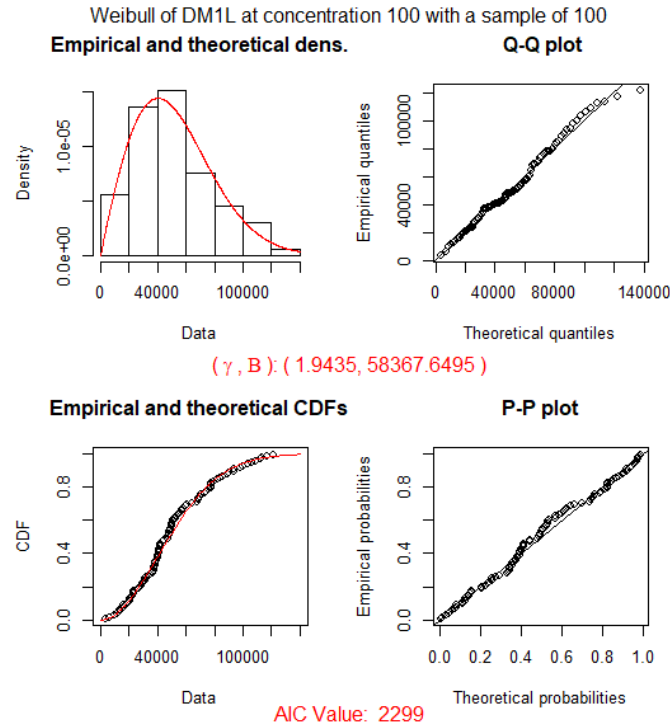


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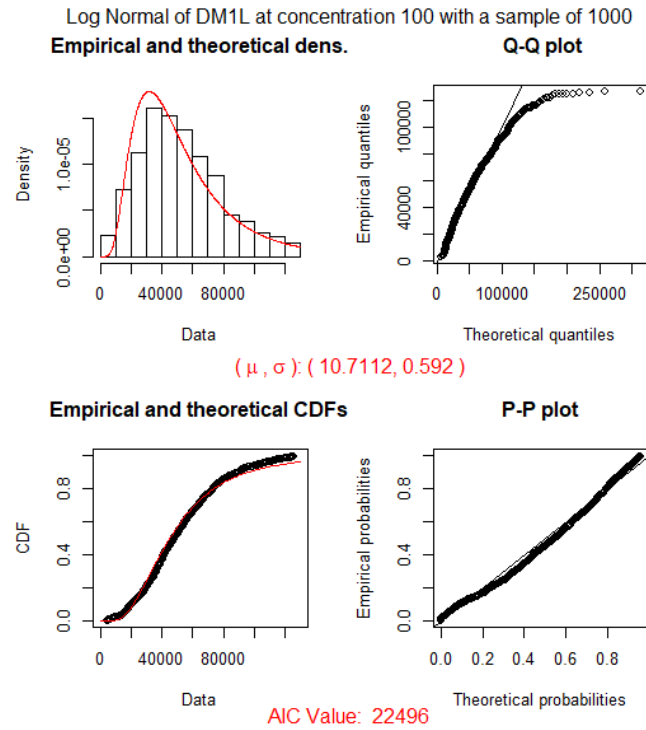


FIGURE 36. The DM1L at concentration 100 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

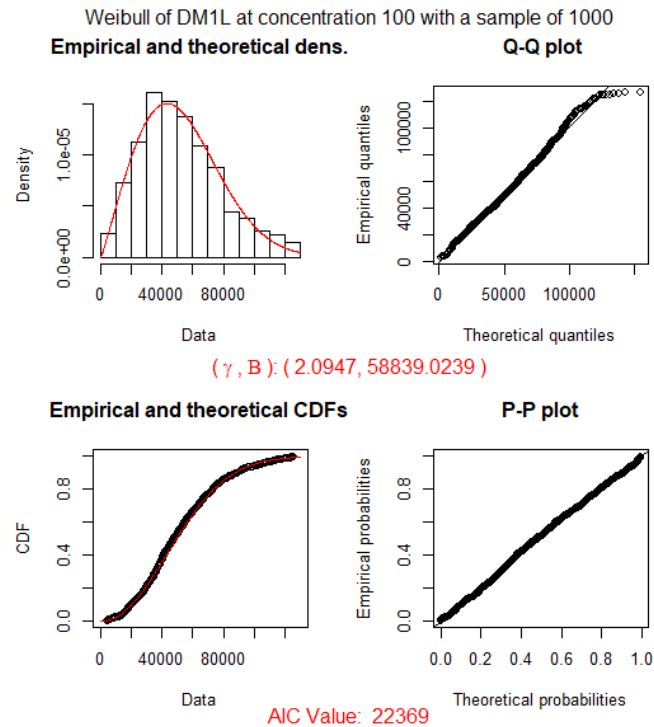


FIGURE 37. The DM1L at concentration 100 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

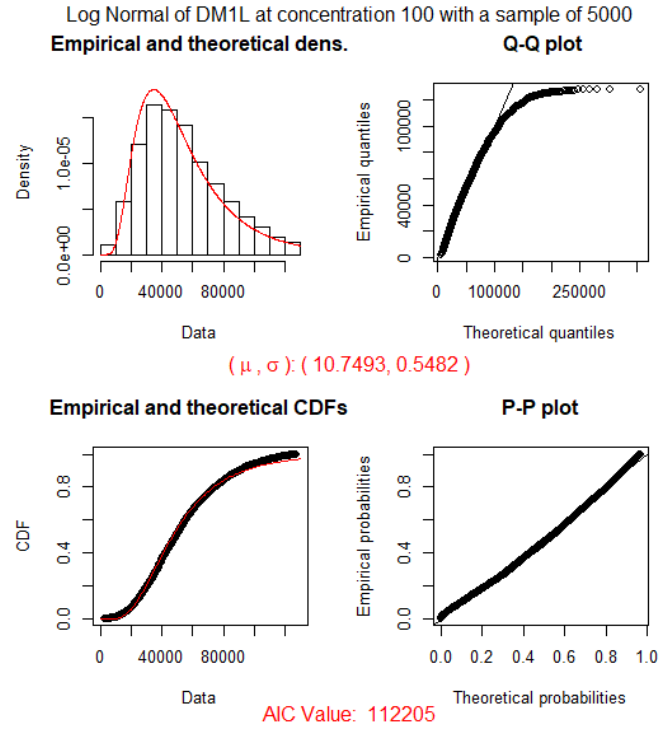


FIGURE 38. The DM1L at concentration 100 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

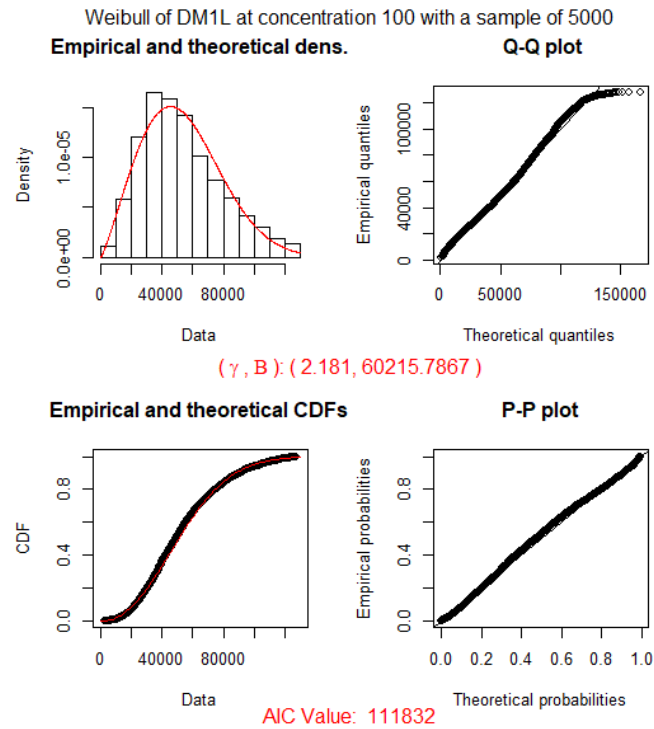


FIGURE 39. The DM1L at concentration 100 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

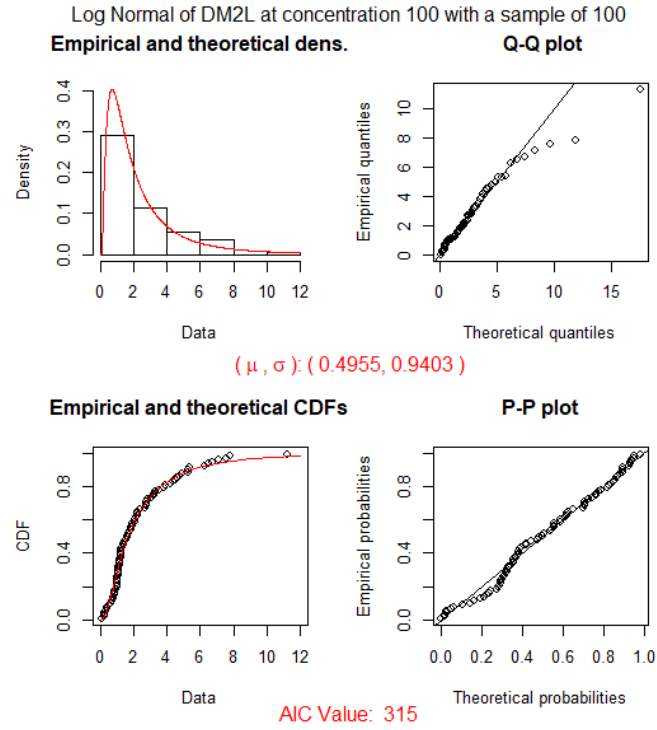


FIGURE 40. The DM2L at concentration 100 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

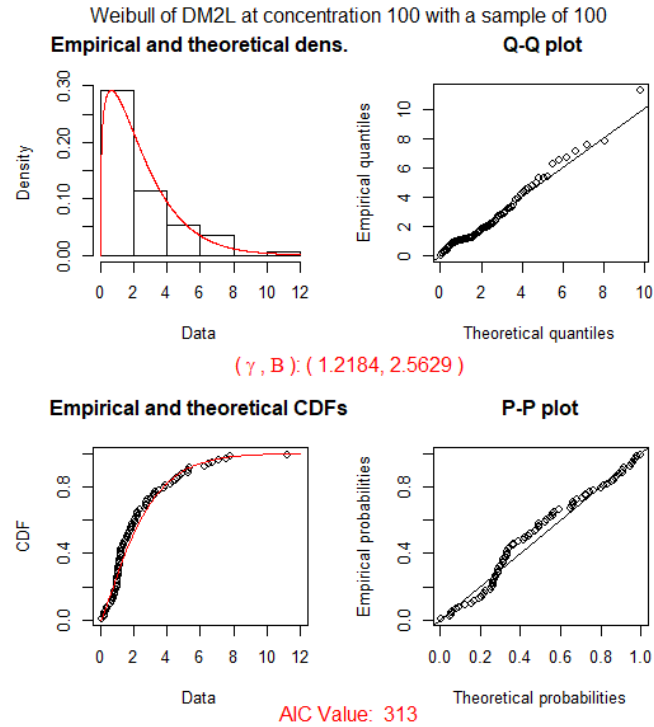


FIGURE 41. The DM2L at concentration 100 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

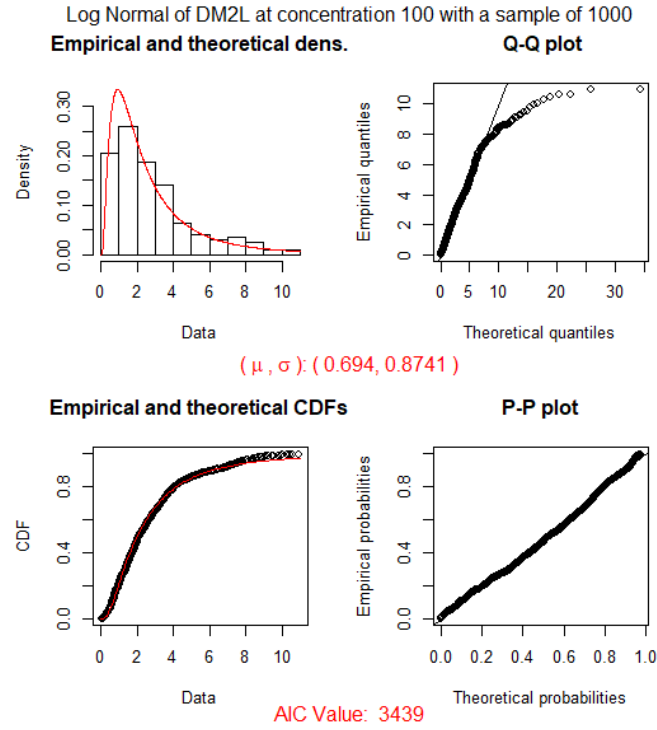


FIGURE 42. The DM2L at concentration 100 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

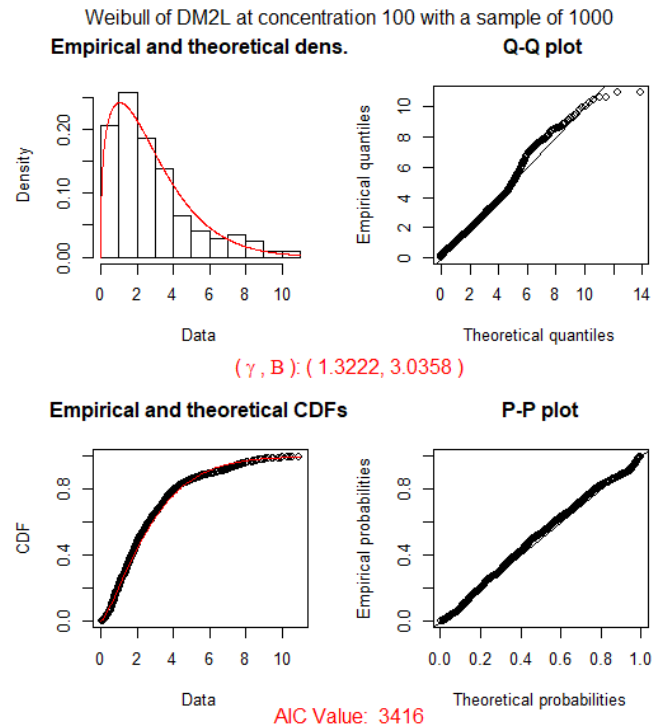


FIGURE 43. The DM2L at concentration 100 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

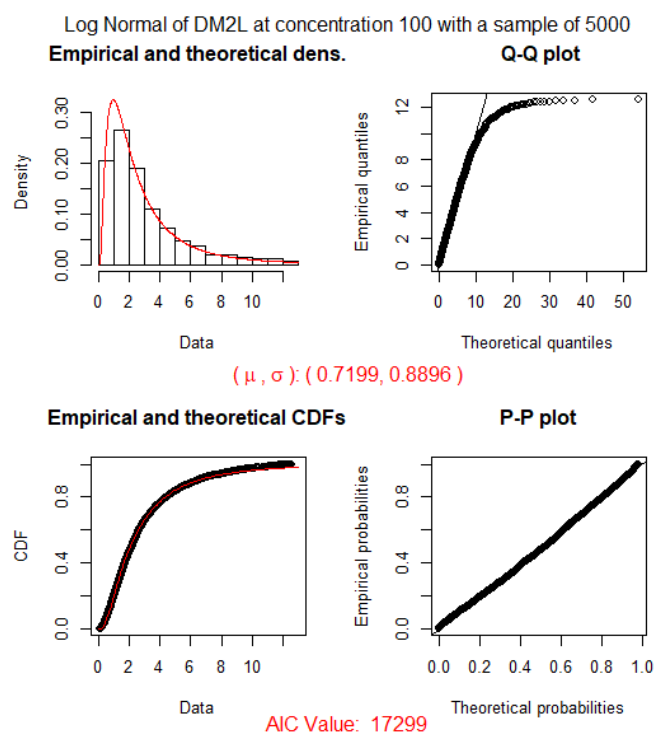


FIGURE 44. The DM2L at concentration 100 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

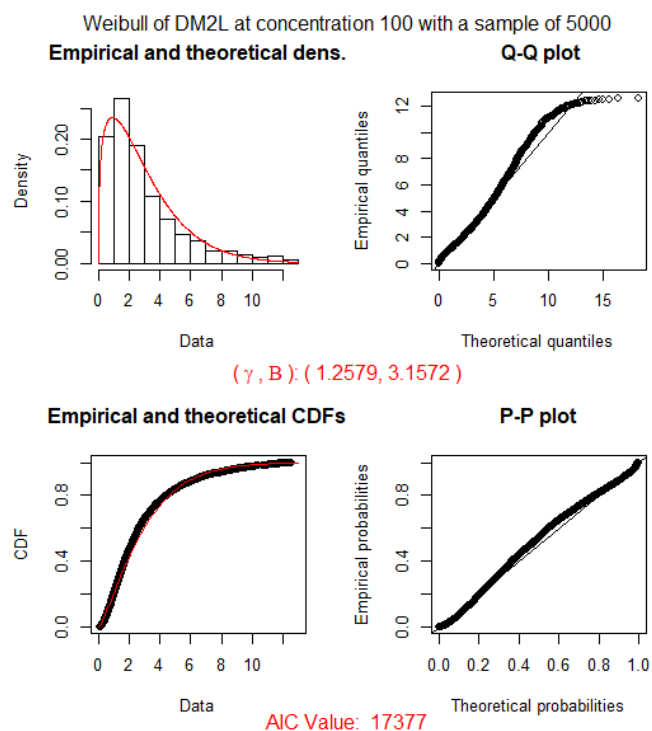


FIGURE 45. The DM2L at concentration 100 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

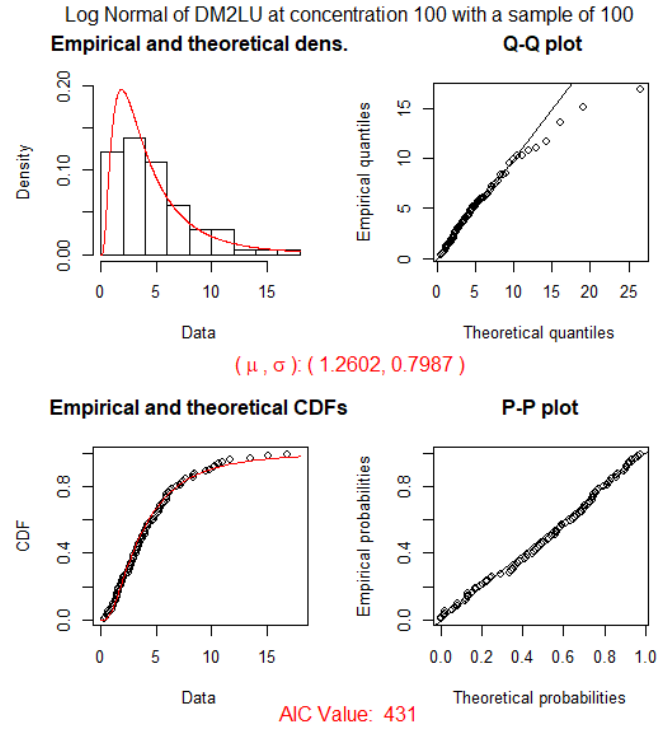


FIGURE 46. The DM2LU at concentration 100 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

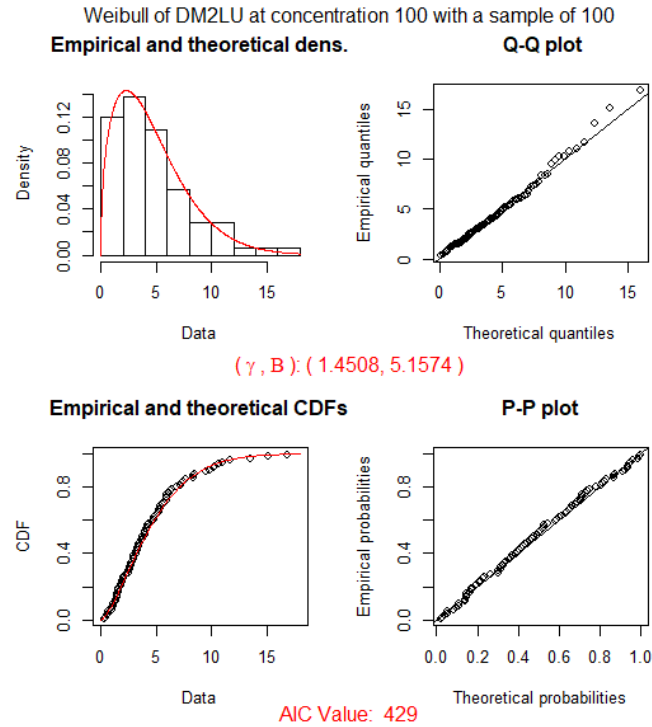


FIGURE 47. The DM2LU at concentration 100 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

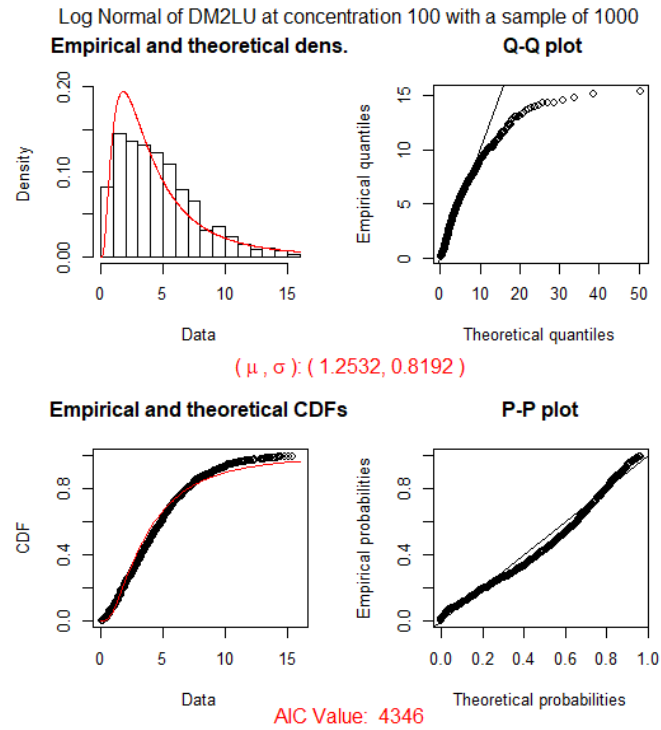


FIGURE 48. The DM2LU at concentration 100 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

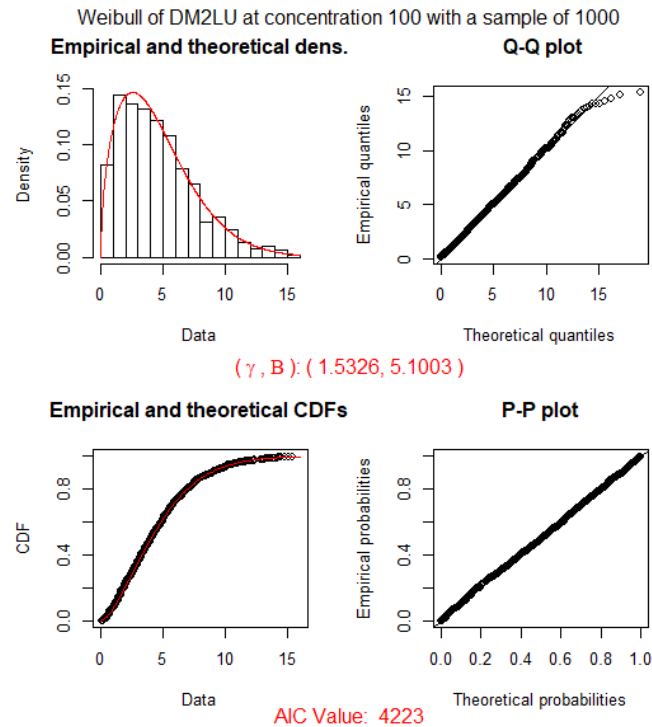


FIGURE 49. The DM2LU at concentration 100 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

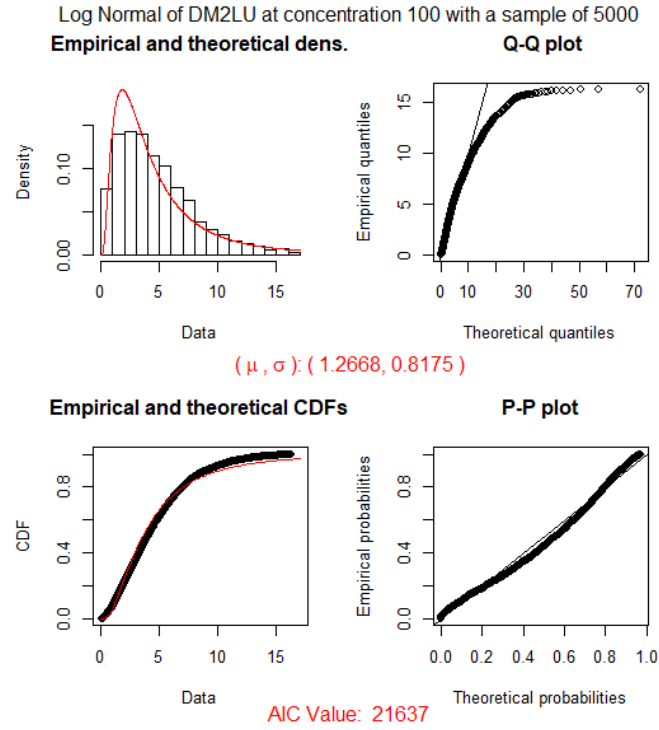


FIGURE 50. The DM2LU at concentration 100 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

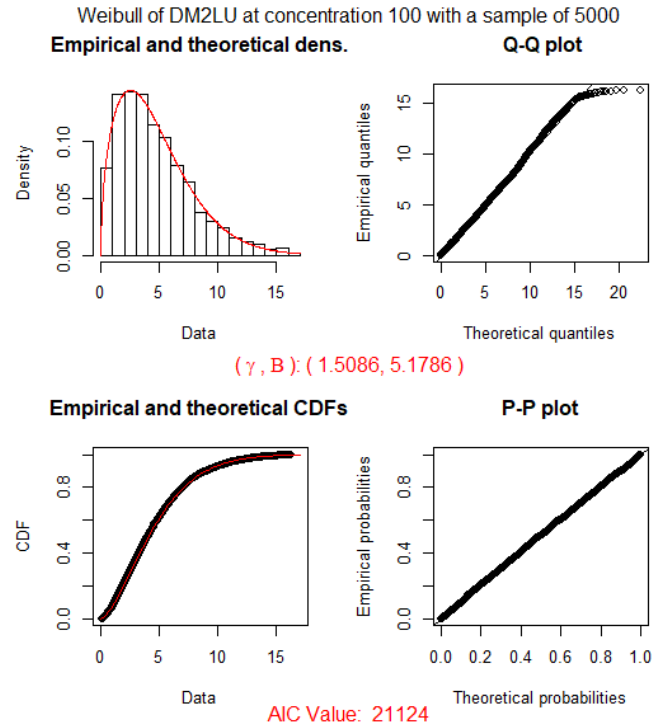


FIGURE 51. The DM2LU at concentration 100 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

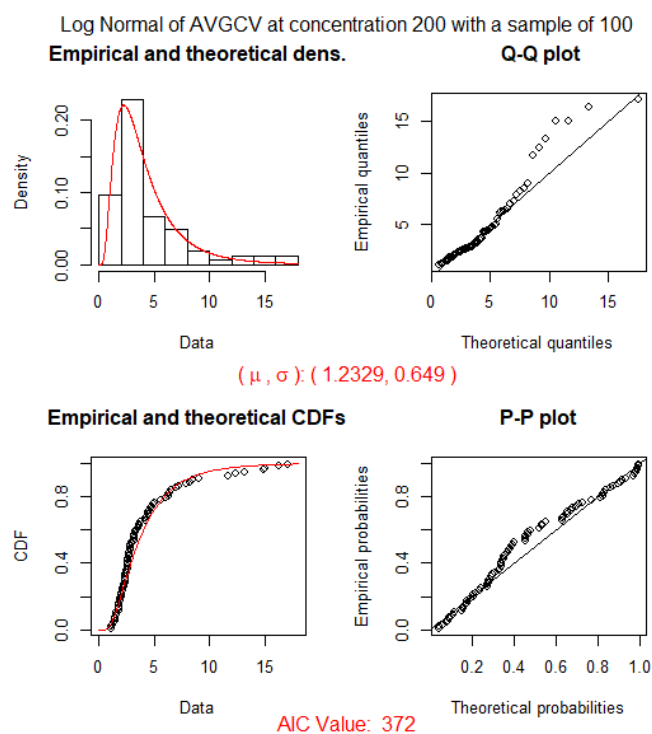


FIGURE 52. The AVGCV at concentration 200 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

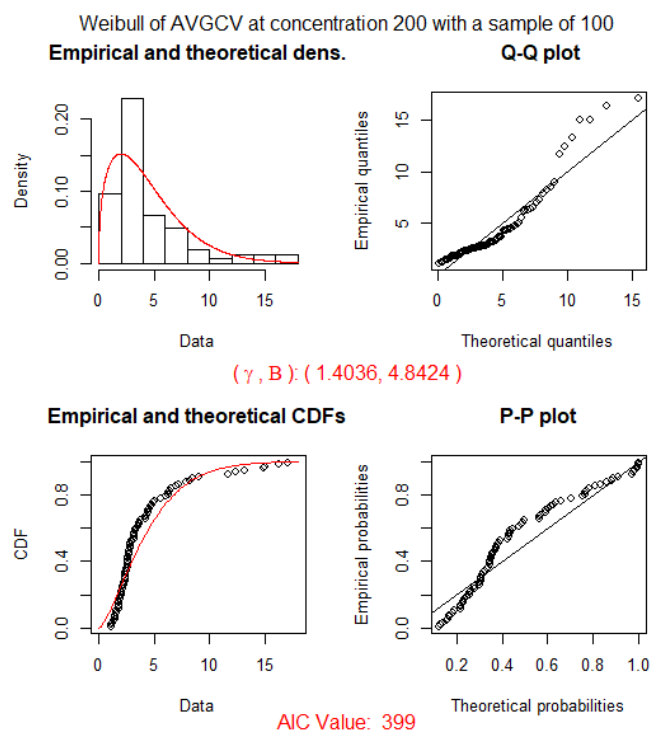


FIGURE 53. The AVGCV at concentration 200 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

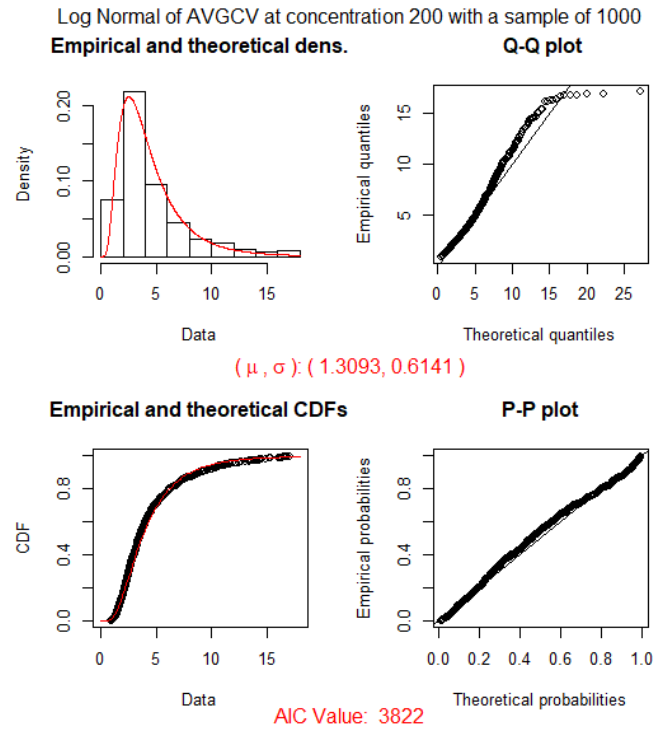


FIGURE 54. The AVGCV at concentration 200 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

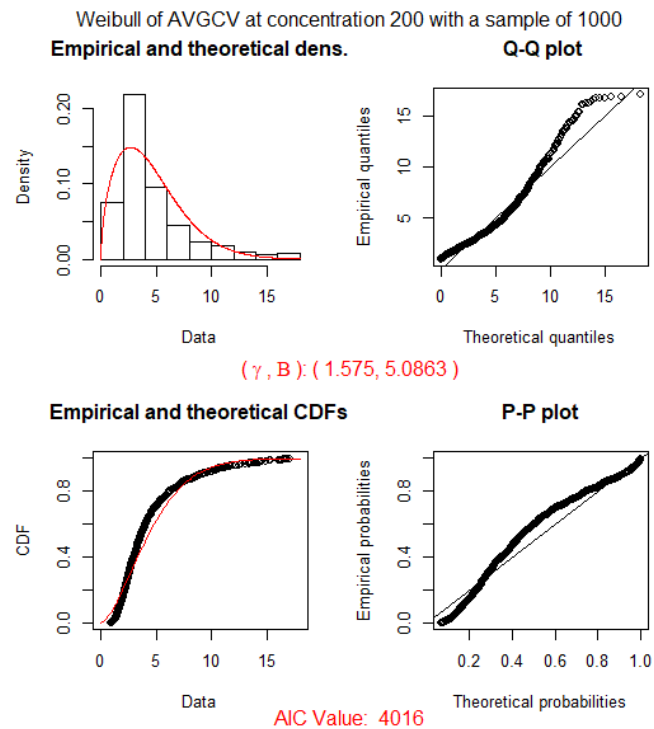


FIGURE 55. The AVGCV at concentration 200 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

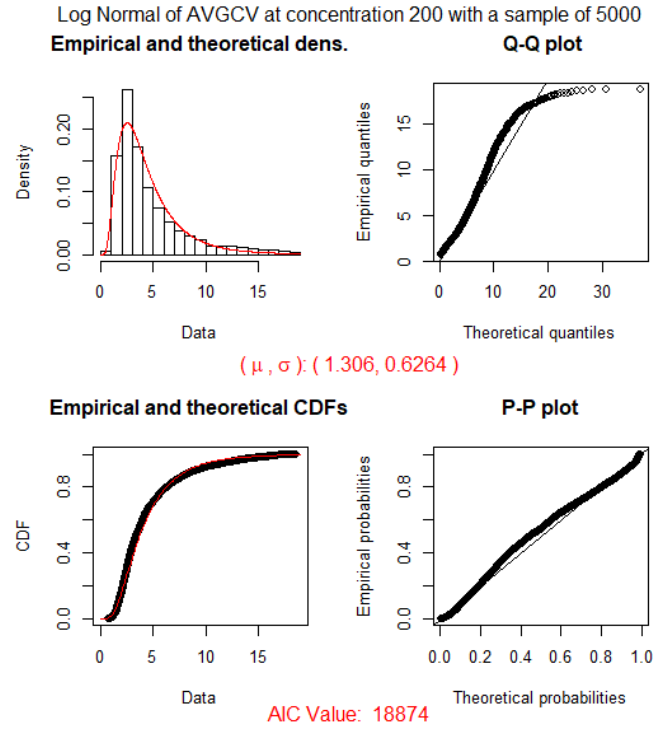


FIGURE 56. The AVGCV at concentration 200 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

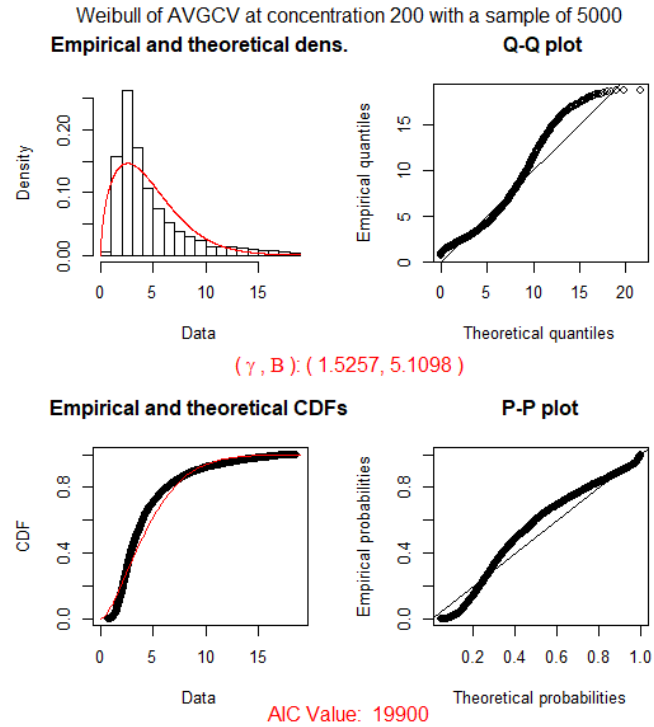


FIGURE 57. The AVGCV at concentration 200 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

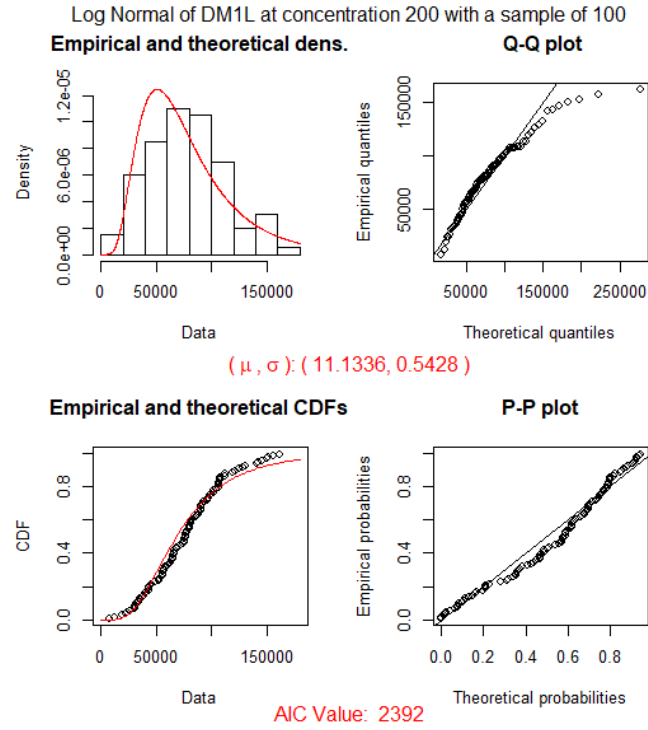


FIGURE 58. The DM1L at concentration 200 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

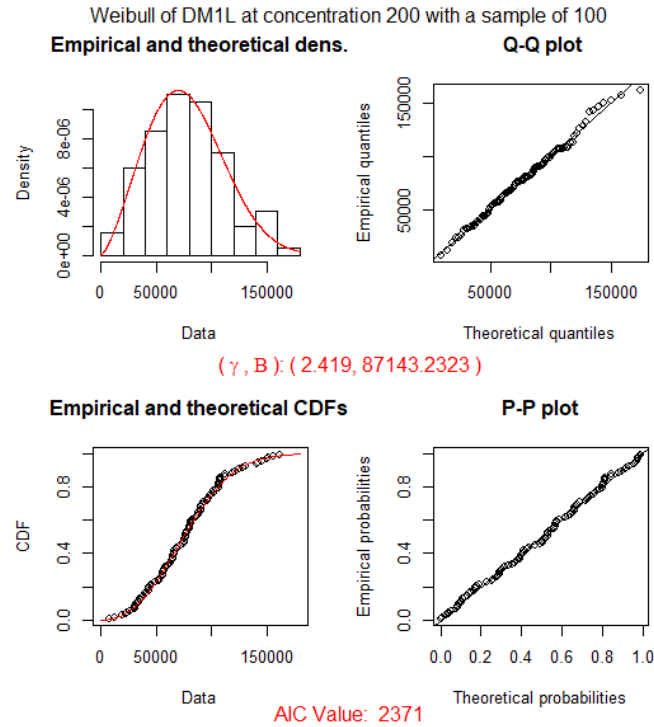


FIGURE 59. The DM1L at concentration 200 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

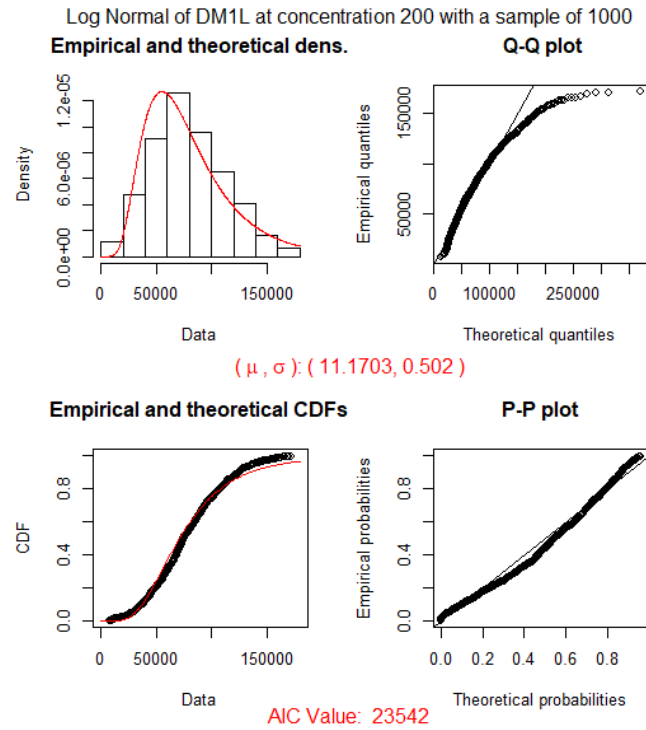


FIGURE 60. The DM1L at concentration 200 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

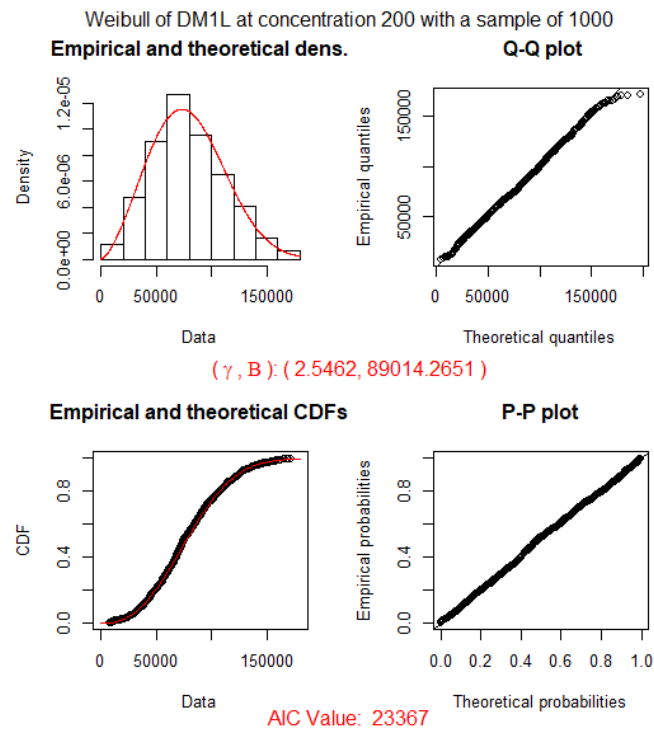


FIGURE 61. The DM1L at concentration 200 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

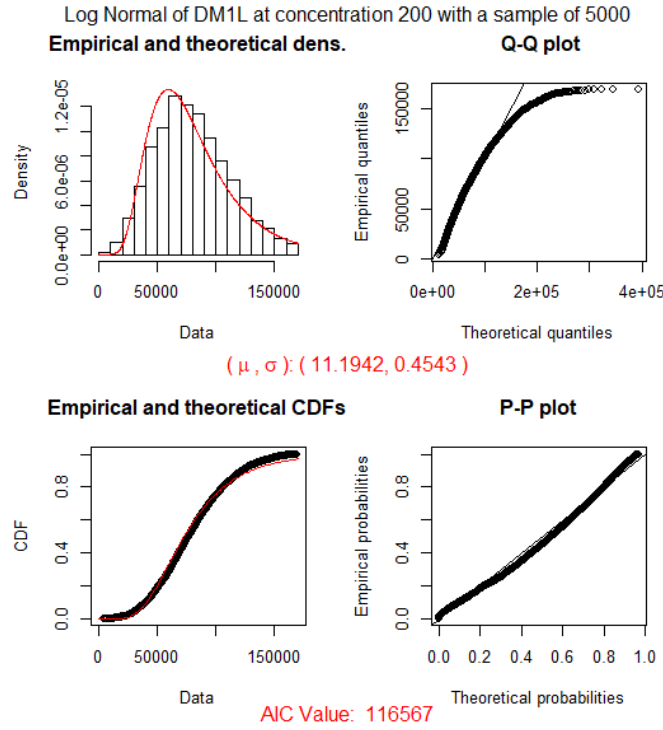


FIGURE 62. The DM1L at concentration 200 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

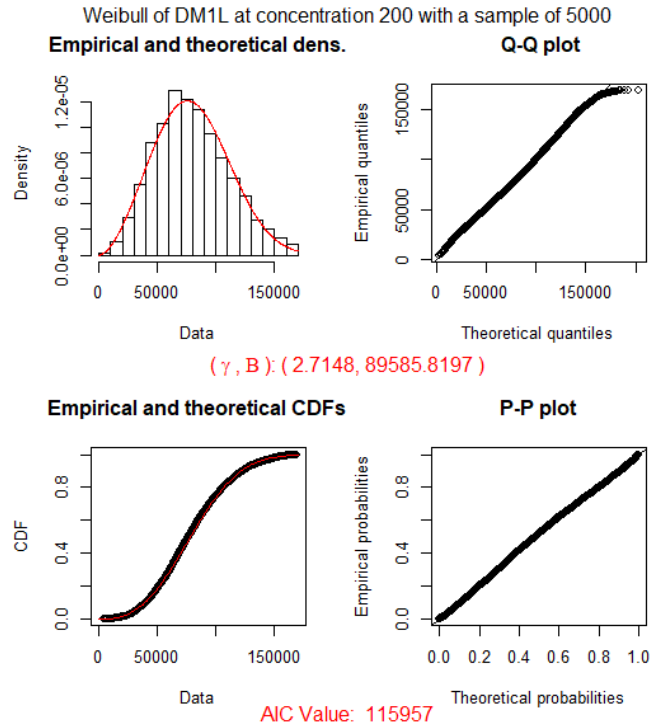


FIGURE 63. The DM1L at concentration 200 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

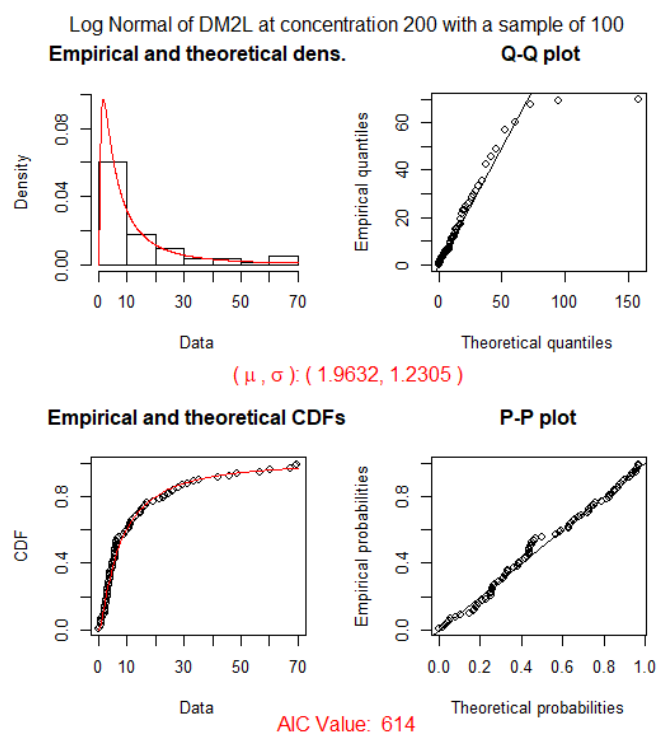


FIGURE 64. The DM2L at concentration 200 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

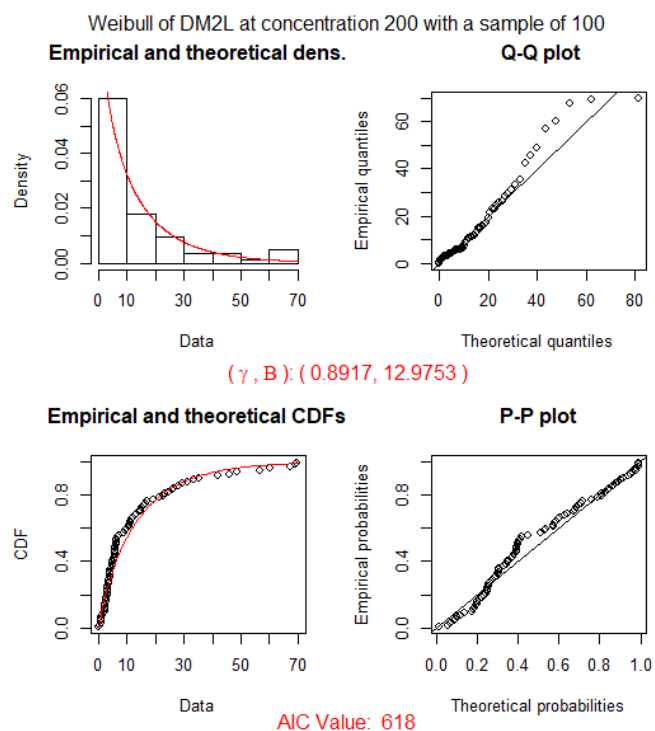


FIGURE 65. The DM2L at concentration 200 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

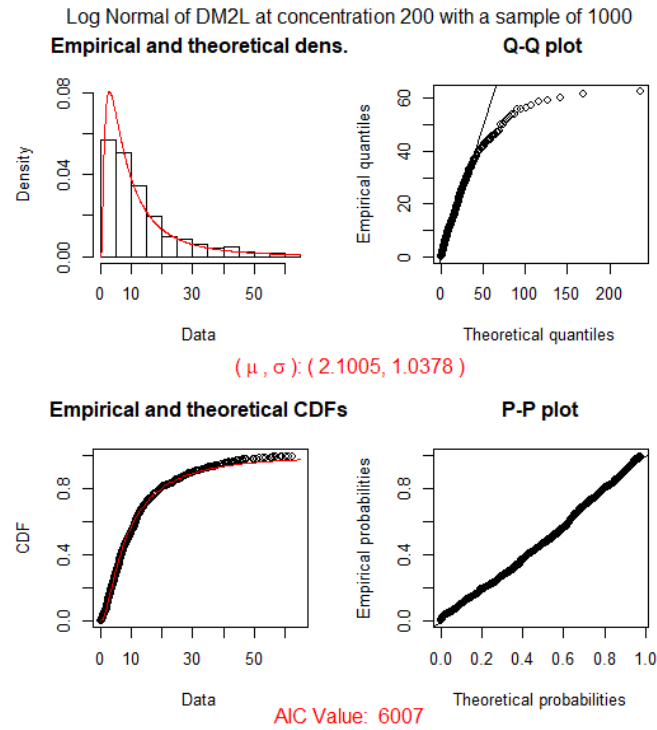


FIGURE 66. The DM2L at concentration 200 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

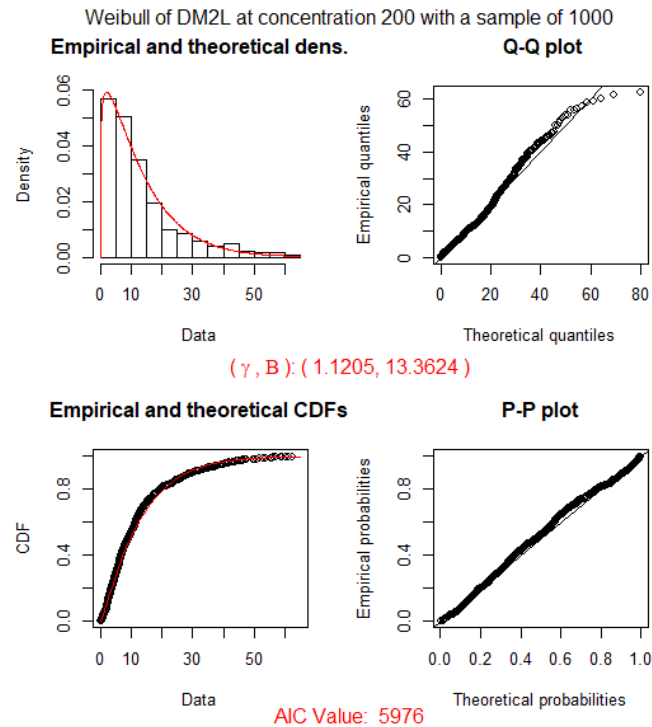


FIGURE 67. The DM2L at concentration 200 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

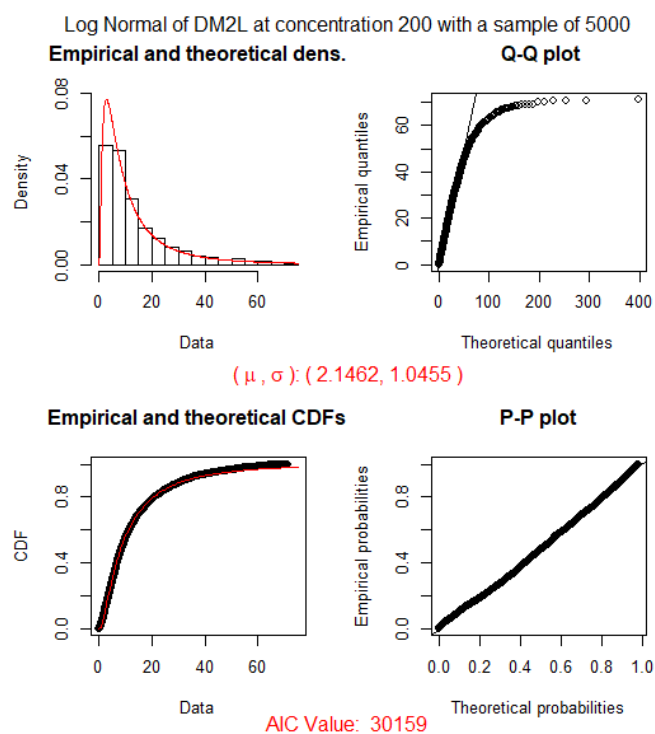


FIGURE 68. The DM2L at concentration 200 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

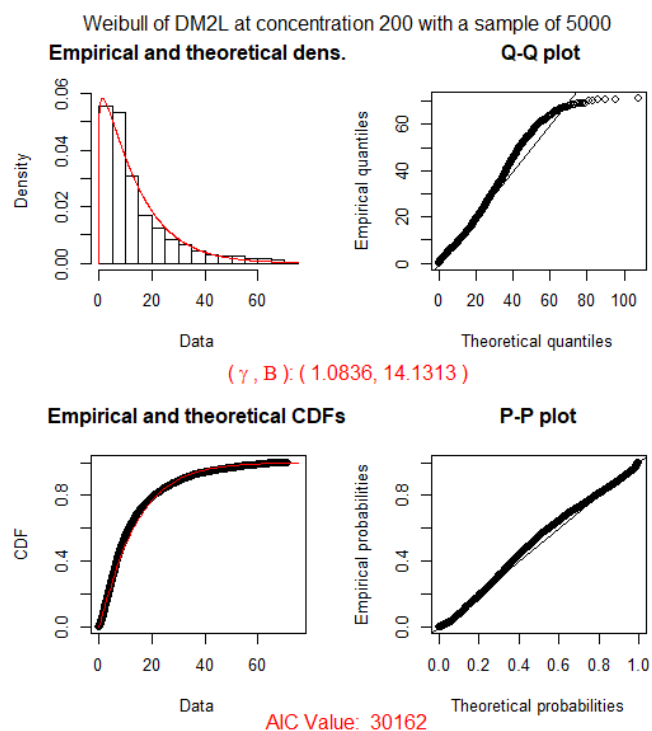


FIGURE 69. The DM2L at concentration 200 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

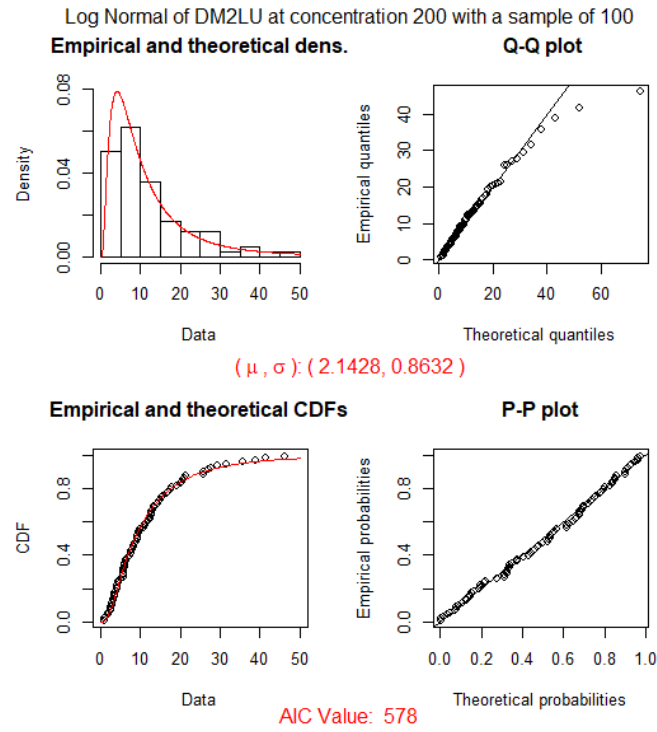


FIGURE 70. The DM2LU at concentration 200 with sample size of 100 with its log-normal distribution fit. Along with parameter estimates and AIC value

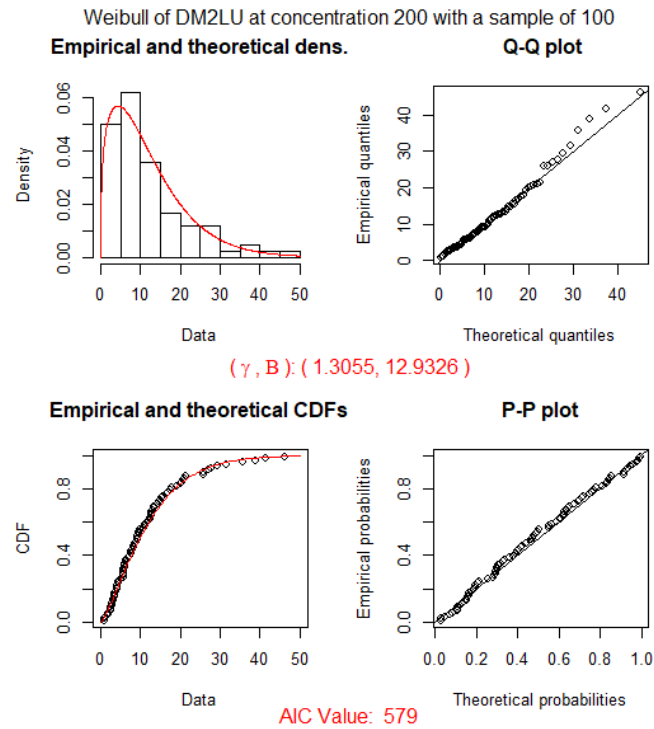


FIGURE 71. The DM2LU at concentration 200 with sample size of 100 with its Weibull distribution fit. Along with parameter estimates and AIC value

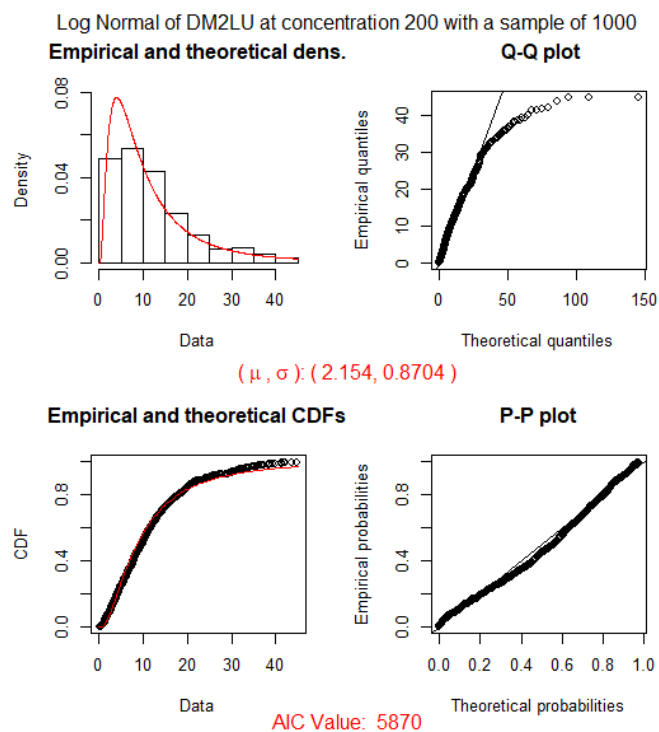


FIGURE 72. The DM2LU at concentration 200 with sample size of 1000 with its log-normal distribution fit. Along with parameter estimates and AIC value

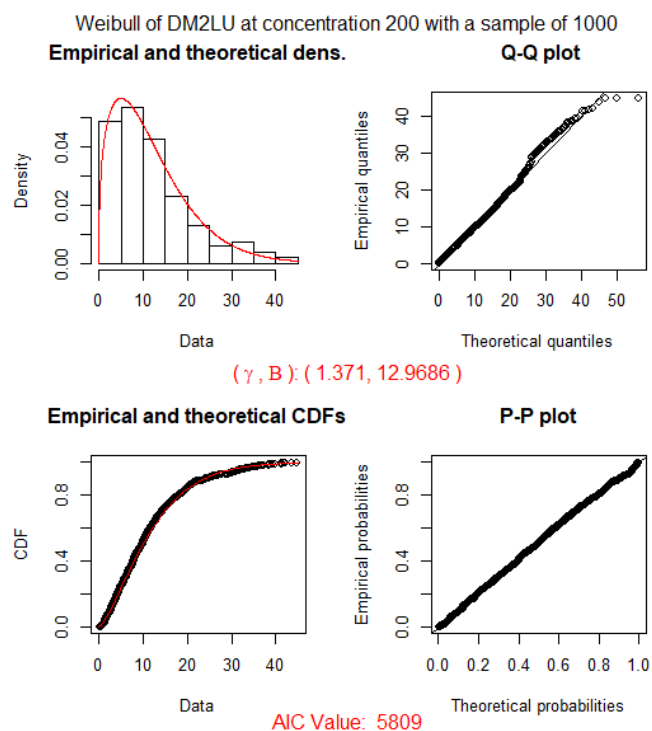


FIGURE 73. The DM2LU at concentration 200 with sample size of 1000 with its Weibull distribution fit. Along with parameter estimates and AIC value

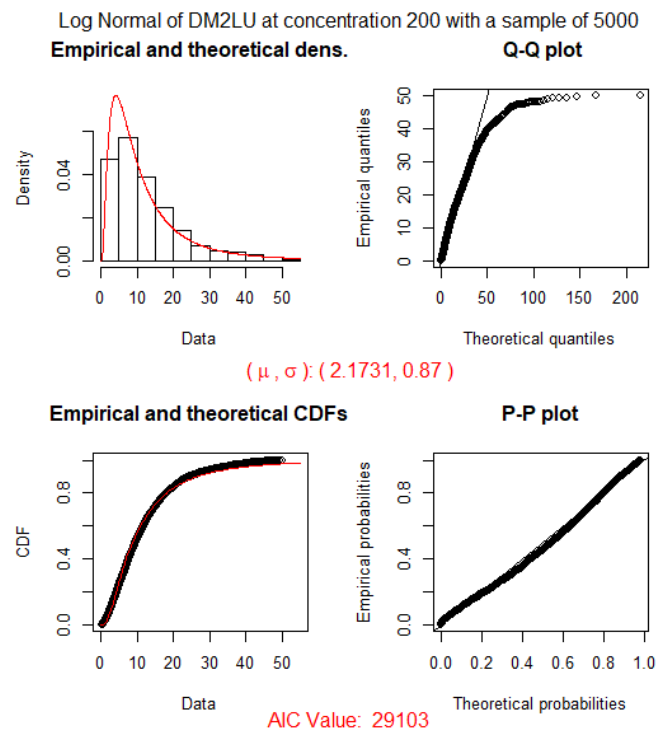


FIGURE 74. The DM2LU at concentration 200 with sample size of 5000 with its log-normal distribution fit. Along with parameter estimates and AIC value

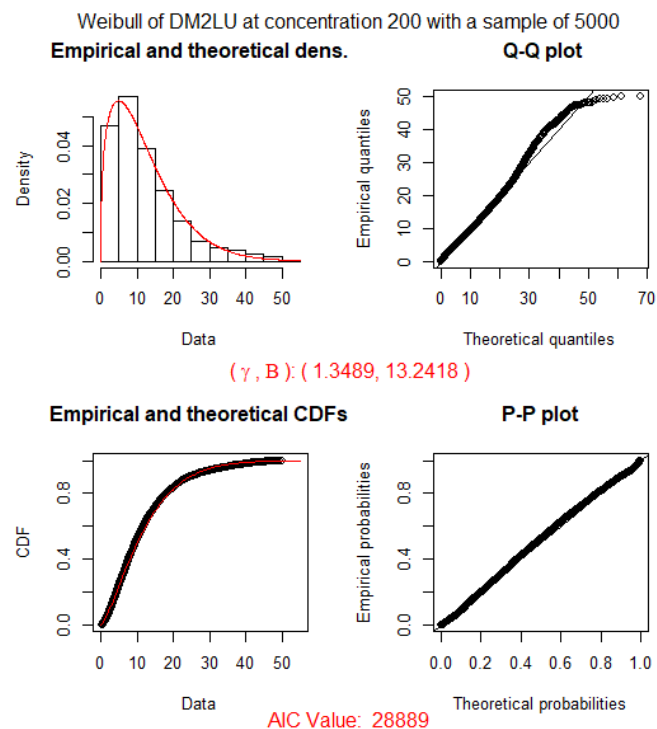


FIGURE 75. The DM2LU at concentration 200 with sample size of 5000 with its Weibull distribution fit. Along with parameter estimates and AIC value

4. CONCLUSION

Based on our analysis of the internal dose metric distributions as depicted above, we have come to the conclusion no one distribution ideally fits all dose metrics uniformly. Rather, specific distributions are better fits for certain dose metrics.

For the dose metrics DM1L, DM2L, and DM2LU, the Weibull distribution offers the best (as in, most uniform) fit for the dose metric data. Even with a sample size as small as 100 for the respective dose metrics, we achieve a reasonable distribution fit for the data with the Weibull distribution.

For the dose metric AVGCV, the log-normal offers the “best” (as in, the most uniform fit for the dose metric data). In contrast to the previously mentioned dose metrics, small sample sizes of the dose metric AVGCV do not produce a reasonable distribution fit of the data.

Our findings from this study will help us achieve our original goal of modeling dose susceptibility in sensitive human subpopulations. We discuss this further shortly.

5. DISCUSSION

Q-Q plots should ideally follow the line on the graph, that is there should be a one to one correspondence with the theoretical quantiles, where the data exists on a log-normal with parameters produced, and the empirical quantiles, where the data actually exists. This would mean that the data closely follows the given distribution. In cases where the empirical quantiles plot deviates greatly from the given line we say that the fitted distribution is not a “good-fit” to the data.

Based upon the results the Weibull works best for the DM1L DM2L and DM2LU dose metrics and lognormal fits slightly better for the AVGCV dose metric. The parameter estimates for each of the fits varies slightly across the different sample sizes, but tends to remain within a reasonable range. More testing would be necessary to determine precise parameter estimates. The sample sizes of 100 are getting results that, depending on the context of a problem, could be substantially close enough to use instead of 5000 samples.

There are many opportunities for future work based off of this research. The distribution fits found for DCM in human interval doses can be replicated with other substances. The ability to analyze other substance’s distributions would allow other toxic materials to be monitored and exposure to humans could be limited.

The human population has subpopulations that are more sensitive to substances that can be toxic. Examples of these sensitive subpopulations are children, elderly people, and pregnant women. These sensitive subpopulations can have different, more sensitive tolerances to substances that can be toxic like DCM. The distributions found for normal human populations can be analyzed to look for sensitive subpopulation characteristics in the distributions. Further research in this area would protect these sensitive subpopulations from over exposure of toxic substances.

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