

# ToxTools

## Software for Dose-Response Modeling, Benchmark Dose Estimation and Risk Assessment

### What is ToxTools?

ToxTools is a complete solution for estimating Benchmark Dose Levels (BMD's), and for modeling and testing data from dose response studies. The package provides modern, sophisticated modeling and estimation algorithms for fitting dose response data as part of a state-of-the-art suite of graphical and numeric analysis tools for toxicological risk assessment.

With ToxTools, you can choose from a variety of standard dose response model forms for binary and continuous responses. Unique to ToxTools are models for multivariate arrays of mixed discrete/continuous endpoints, as well as the ability to accommodate correlated data such as that arising in studies of litters or clusters.

Quantitative risk estimation based on the popular Benchmark Dose methodology is easily achieved from any of the available dose response models, including recent methodological advances for defining risk from multiple outcomes. In addition to classical procedures for conducting group comparisons and tests of trend, the software incorporates new methodology for exact trend tests that apply in cases where sample sizes are small.

ToxTools incorporates these features in an intuitive, friendly Windows environment that was specifically designed for flexibility and "what if" calculations. It is very easy to conduct multiple analyses at both the modeling and risk estimation stages in order to compare/

contrast results. And like all of Cytel's products, the package attains the highest quality of commercial standards for reliability, documentation and customer support.

### Who needs ToxTools?

If your work involves testing the safety of chemical or environmental agents, assessing the efficacy of pharmaceutical agents, analyzing and fitting curves to dose-response data, or computing benchmark doses, then you need ToxTools.

### Who Developed ToxTools?

ToxTools was developed as a joint effort by scientists at Harvard University, the Dana-Farber Cancer Institute, and Cytel Software Corporation, with funding support from the National Cancer Institute. Leadership for this project was provided by Professors Louise Ryan and Paul Catalano, who are part of the Environmental Statistics Program at the Harvard School of Public Health.

### Features of ToxTools

- Availability of all standard dose response models (one-hit, logit, probit, Weibull and more).
- Linear, polynomial and power regression models for continuous outcomes.

- Dose response assessment of simultaneous and hierarchical multiple outcomes.
- Analysis of correlated data using generalized estimating equations (GEE).
- Trend and pairwise tests for binary or continuous outcomes.
- Exact tests of trend for both uncorrelated and correlated outcomes in small data sets.
- Single and multiple outcome risk estimation using Benchmark Dose methodology, with several methods for lower limit calculations.
- Simple dialogs for model specification, intelligent recall to modify previous runs and check sensitivity to modeling assumptions.
- Data summarization and exploratory graphics, tailored to the analysis of dose response data.
- Workbook-style interface for organization and comparison of results.
- Publication quality graphics.
- Powerful, Excel-like data editor with variable creation, transformation, and case subsetting.
- Imports SAS, EGRET, ASCII, NTP and many other file formats.

## Example 1: Developmental Toxicology

A developmental toxicology study looked at 1142 individual live fetuses born to 102 pregnant mice exposed to 0, 0.25, 0.5 or 1.0 unit of a chemical. Table 1 shows the summary data, and indicates malformation rates increasing from 0.31% in the control group to 12.59% in the highest dose group. Live fetuses (individuals) belonging to a single mother constitute a cluster. Switching from unclustered to clustered analysis is as easy as checking one box in ToxTools – see Figure 1.

Table 1. Summary Data on Malformation Rates

Dose	No. Clusters	No. Individuals	Percent Response
0	27	319	0.31%
0.25	26	275	1.09%
0.5	26	262	1.15%
1	28	286	12.59%

From the ToxTools Model-Fit menu, which features a rich class of dose-response models, the Probit model was chosen for these data (Figure 1). Malformation (Malf) is the outcome variable, Dose the predictor variable, and ClusterID the cluster variable.

Figure 1. Dialog Box for Model Fitting

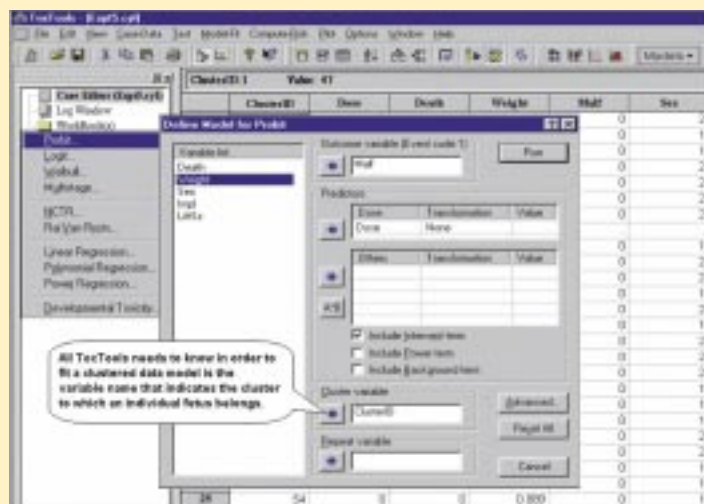


Table 2 shows the results from fitting the probit model. The results show a highly significant dose effect.

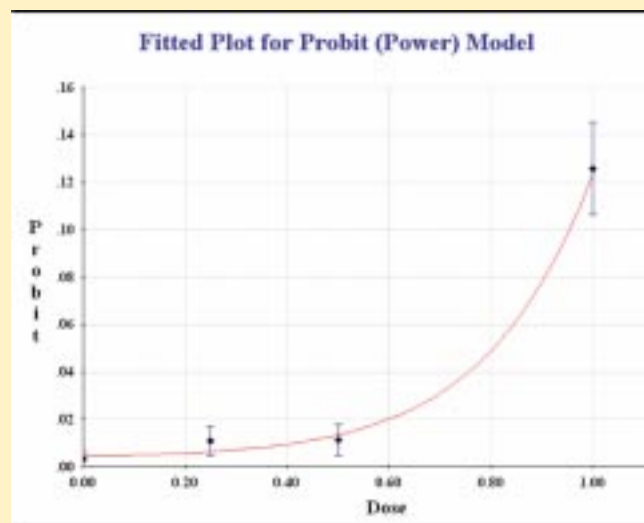
Table 2. Parameter Estimates

Probit Model ( Based on 1142 individuals in 102 clusters )				
Model	P( Malf = 1 ) ~F(Predictor)			
	Predictor = %Intercept + Dose			
	F(x) = Φ(x)			
Parameter Estimates				
Parameter	Estimate	Std Err	z-value	p-value
%Intercept	-2.9056	0.3197	-9.0875	< 0.0001
Dose	1.7290	0.3910	4.4215	< 0.0001

## Can the Model Be Improved?

With ToxTools, you can easily fit alternative models to your data. Fitting a power model  $P(\text{malf}) = \Phi[a + b \cdot (\text{dose})^g]$ , resulted in a strong nonlinear fit, reflecting closely the pattern seen in Table 1, where the response rates stayed fairly flat for the lower dose levels and increased markedly at the highest dose (Figure 2).

Figure 2. Fitted Plot for the Power Model



## Benchmark Dose Estimation

The excess risk estimates can now be computed from the power model. ToxTools allows us to easily find a BMD and a BMDL (the dose level and associated lower confidence limit linked with a specified level of risk)

Figure 3. Plot of Excess Risk Estimates

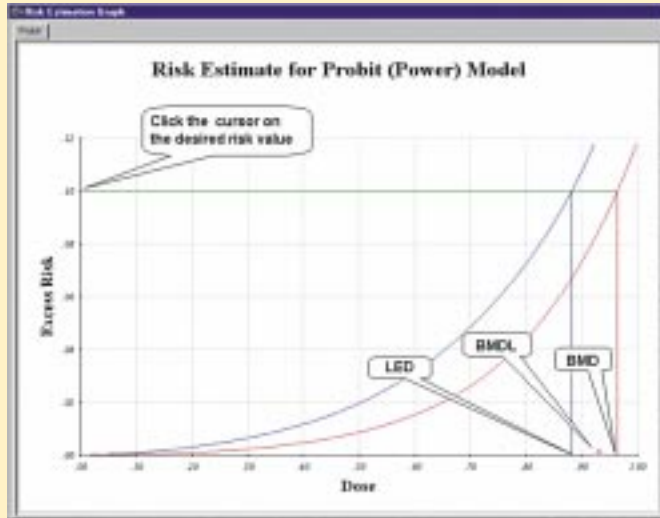


Figure 3 shows that, at an excess risk level of 0.1, the BMD is 0.964, the BMDL is 0.931, and the Lower Effective Dose (LED) level is 0.882.

## Joint Continuous and Binary Outcomes

The example just cited was for binary data. ToxTools deals just as easily with continuous data. And suppose your analysis must incorporate both binary and continuous outcome data — for example, fetal malformation and fetal weight among live animals in the developmental toxicity context. No problem — with ToxTools you can specify and fit the appropriate multivariate model (Figures 4 and 5).

Figure 4. Developmental Toxicity: Dialog Box

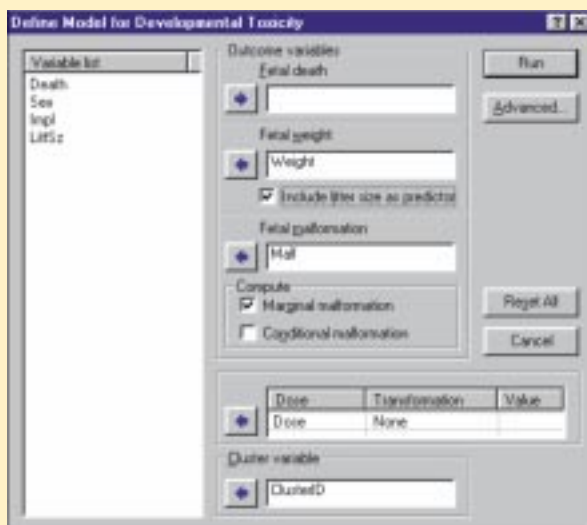
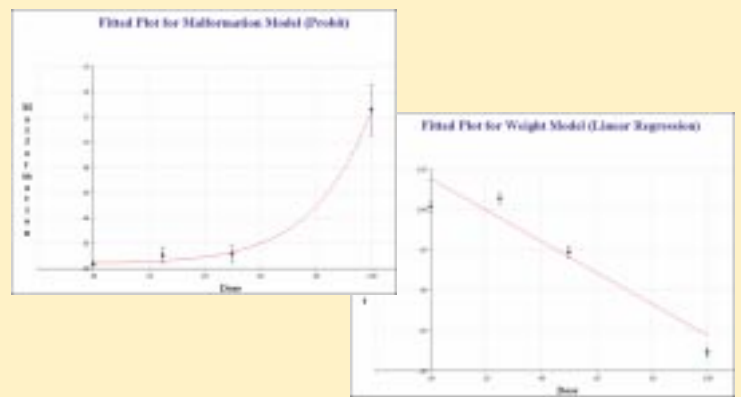
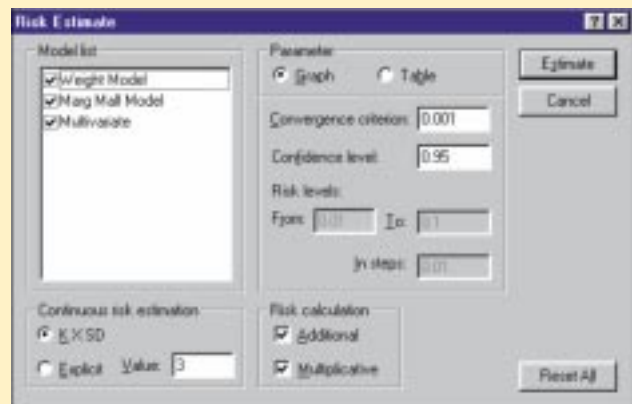


Figure 5. Developmental Toxicity: Fitted Plots



For the above Developmental Toxicity analysis, the risk estimates for the Weight Model, the Marginal Malformation Model and the Multivariate Model in both graphical and tabular form can be obtained through the dialog box shown in Figure 6.

Figure 6. Developmental Toxicity: Risk Estimates



## Example 2: Tests of Trend

A study, conducted in mice, tested a potentially harmful drug at the following doses: 0, 1, 10, 100 mg/kg. There were 96 litters with a total sample size of 1248. Table 3 displays the binary response rates at different dose levels, which increase from 1.39% at control level to 3.05% at the highest dose level.

Table 3. Summary Data on Response Rates

Dose	No. Clusters	No. Individuals	Percent Response
0	24	288	1.39%
1	25	327	1.83%
10	23	305	2.62%
100	24	328	3.05%

Now the question is whether this trend in the response rates is statistically significant. Figure 7 shows the different options available in ToxTools for trend and pairwise tests.

Figure 7. 'Test' Menu

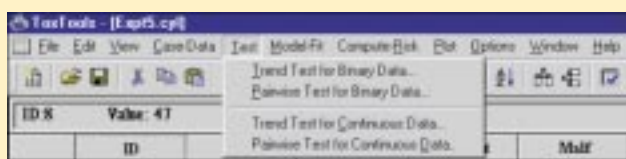
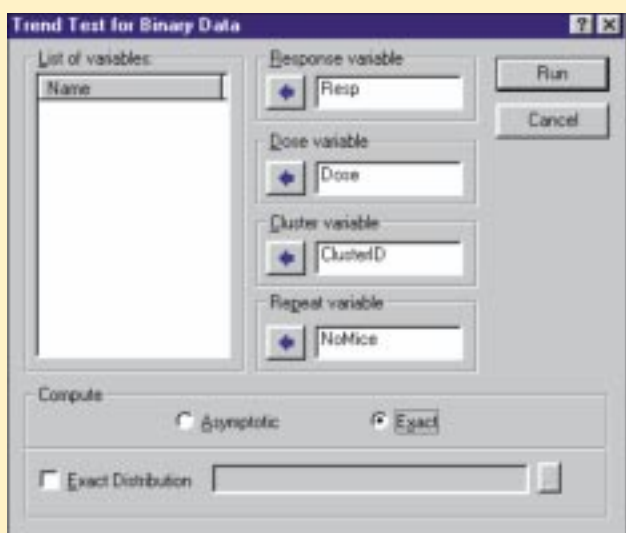


Figure 8 shows the dialog box after the variables are appropriately allotted to different categories. Notice again that the correlation due to clustering is automatically accounted for simply by specifying the cluster variable (clusteredID) in the appropriate box.

Figure 8. Trend Test: Dialog Box



The results obtained from running the trend test are given in Table 4. Two asymptotic and one exact test were computed.

Table 4. Trend Test: Results

Inference Method	Min	Max	Mean	SD	Observed	Stdized	Tail	P-Value	
								1-sided	2-sided
Rao-Scott	(NA)	(NA)	0.0223	289	255	1.220	Right	0.111	0.223
GEE-Score	(NA)	(NA)	0	323	274	0.848	Right	0.198	0.396
Exact	0	2800	739	222	1090	(NA)	Right	0.059	0.115

Note the considerable difference in the p-value obtained from the exact method ( $p = .059$ , 1-sided), compared to the p-values obtained from the two asymptotic methods ( $p = .111$ , 1-sided, Rao-Scott and  $p = .198$ , 1-sided, GEE score). Despite the large overall sample size, you can see that the unequal spacing of dose levels, as well as the low response rates, lead to this discrepancy between the exact p-value and the p-values obtained through asymptotic approximations.

## What the Experts Say About ToxTools

“...ToxTools may provide one of the most accessible set of tools for deriving risk estimates for clustered toxicology data.” —*John Bailer, Dept. of Mathematics and Statistics, Miami University and co-author of Statistics for Environmental Biology and Toxicology.*

“ToxTools is unique in having a wide range of models, including GEE- based developmental toxicity models and joint outcome models. The model explanations in the manual are complete, and the on-line help is very useful. The interface is intuitive, consistent, and quickly learned.” —*Mark J. Nicolich, Statistician, ExxonMobil Biomedical Sciences, Inc.*

“This is a great software package for designing and analyzing toxicological experiments. What previously took quite some time to program myself is now readily available in ToxTools.” —*Stephan Ogenstad, Director, Biometrics, Vertex Pharmaceuticals Inc. Cambridge, Massachusetts.*

## Technical References

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