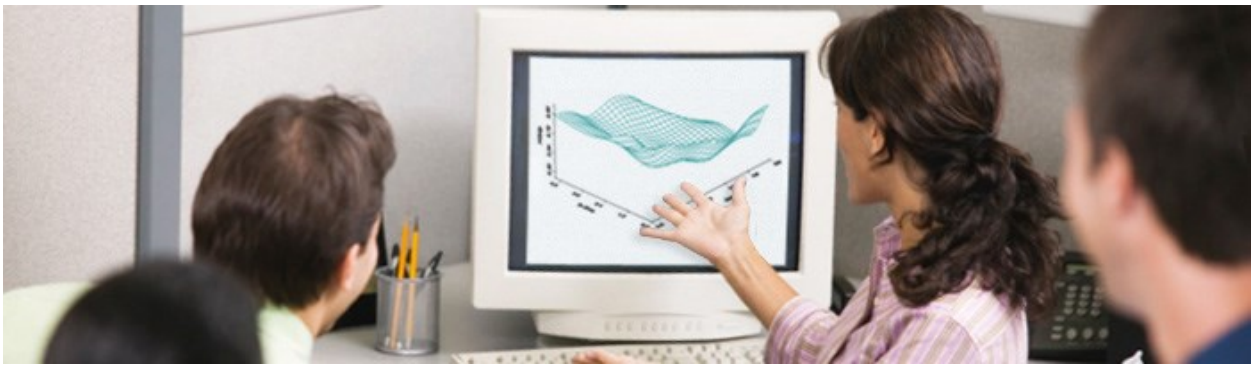


BENCHMARK DOSE SOFTWARE (BMDS)

USER MANUAL

Developed for

EPA United States Environmental Protection Agency

TABLE OF CONTENTS

OVERVIEW

The U.S. Environmental Protection Agency (EPA) Benchmark Dose Software (BMDS) was developed as a tool to facilitate the application of benchmark dose (BMD) methods to EPA hazardous pollutant risk assessments. This help file provides instruction on how to use the BMDS, but is not intended to address the EPA BMD methods. However, every attempt has been made to make this software consistent with EPA Risk Assessment Forum (RAF) Benchmark Dose Technical Guidance Document (U.S. EPA, 2012).

HISTORY OF BMDS DEVELOPMENT

Research into model development for BMDS started in 1995 and the first BMDS prototype was internally reviewed by EPA in 1997. After external and public reviews in 1998–1999, and extensive Quality Assurance testing in 1999–2000, BMDS version 1.2 was released in April, 2000. Subsequent versions were released up to version 1.4.1b in August 2007. BMDS version 2.3.1 featured a revamped user interface and new dichotomous models ("Dichotomous Alternative" model type).

A history of the versions of BMDS released by EPA is contained in the Version History appendix.

The models contained in the current version of BMDS are listed in the Model Descriptions section of this file.

HOW EPA USES BMD METHODS

EPA uses BMD methods to estimate reference doses (RfDs) and reference concentrations (RfCs), which are used along with other scientific information to set standards for noncancer human health effects.

Prior to the availability of tools such as BMDS, risk assessment benchmarks such as RfDs and RfCs were determined from no-observed-adverse-effect levels (NOAELs), which represent the highest experimental dose for which no adverse health effects have been documented.

However, using the NOAEL in determining RfDs and RfCs has long been recognized as having limitations:

- It is limited to one of the doses in the study and is dependent on study design

- It does not account for variability in the estimate of the dose-response
- It does not account for the slope of the dose-response curve
- It cannot be applied when there is no NOAEL, except through the application of an uncertainty factor (Crump, 1984; Kimmel and Gaylor, 1988).

A goal of the BMD approach is to define a starting point of departure (POD) for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design. The EPA Risk Assessment Forum has published technical guidance for the application of the BMD approach in cancer and non-cancer dose-response assessments (U.S. EPA, 2012).

Using BMD methods involve fitting mathematical models to dose-response data and using the different results to select a BMD that is associated with a predetermined benchmark response (BMR), such as a 10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain.

BMDS facilitates these operations by providing simple data-management tools and an easy-to-use interface to run multiple models on the same dose-response dataset. Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and the estimate of the lower-bound confidence limit on the BMD (BMDL). Model results are presented in textual and graphical output files that can be printed or saved and incorporated into other documents.

RUNNING A BMDS SESSION

Running the models on a dataset consists of five basic steps.

- Step 1: Create a new session or open an existing session.
- Step 2: Select the appropriate models based on the type of dataset being evaluated.
- Step 3: Create a dataset using the BMDS spreadsheet capability or import a data file.
- Step 4: Specify the parameters associated with the model selected by choosing or creating a new option file.
- Step 5: Run the Model and view the tabular and graphical results.

FUTURE OF BMDS

EPA plans to continually improve and expand the BMDS system.

Use the BMDS web page as your most up-to-date source of information and updates pertaining to the BMDS. The entire BMDS system or model updates can be downloaded from the web site. The source code files for the models used in the BMDS system are also available via the BMDS web site to reviewers and programmers who might be interested in performing an in-depth analysis of the model algorithms and features.

We welcome and encourage your comments on the BMDS software and the model source code files. Please provide comments, recommendations, suggested revisions, or corrections through our Help Desk Form. Once in the BMDS system, if you have problems or concerns, please use the "Problem Report" feature listed in the BMDS "Help" menu.

References

- Crump, K. 1984. A new method for determining allowable daily intakes. Fund. Appl. Toxicol. 4: 854–871.
- Kimmel, C.; Gaylor, D. 1988. Issues in qualitative and quantitative risk analysis for developmental toxicology. Risk Anal. 8: 15–21.
- U.S. EPA. 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460: EPA/100/R-12/001, June 2012.

USING BMDS 2.6.0.1

SETTING UP BMDS 2.6.0.1

SYSTEM REQUIREMENTS

- BMDS requires at least 16 Megabytes of RAM and should run in Microsoft Windows 2000, NT, XP, Vista, 7, and 8, however only operation in Windows XP has been fully tested at this time. BMDS Version 2.6.0.1 can be installed in any folder where the user has create/read/write privileges.
- BMDS also requires the latest version of .NET (4.0 or later). If your machine is set up to allow or be notified of downloads of Microsoft software, then it is likely that that version of the .NET framework is already installed. Otherwise, the latest version of .NET for client desktops can be downloaded from the Microsoft site.
- To run the ToxicoDiffusion model included in this version of BMDS, you must download and install the 32-bit edition of version 3.1 or later of the R statistical software to your computer.

DETERMINING WHETHER BMDS IS PROPERLY INSTALLED

The following procedure will help you determine whether the BMDS components have properly loaded and the application is working as expected.

1. Start BMDS.
2. From the BMDS application menu, choose File>Open>Dose Response Session (.ssn). The Open File dialog box should display the contents of the BMDS SessionFiles folder.
3. Select and open any .ssn file (e.g., Cancer-BMR10.ssn). The Session screen should appear.
4. Click the Save As button and resave the session under a different name (e.g., Cancer-BMR10-test.ssn; you can delete this file later).
5. Click the Run button on the Session screen. Plots and a summary report should appear.
6. At the top of the summary report screen, select File>Export to Excel. Pre-selected summary report data should export to several Excel worksheets, with the “Dichotomous Format” or Continuous Format” worksheet in the initial view.

If you are able to complete the above steps without difficulty (aside from normal model error messages), BMDS is likely to be installed properly and completely.

Note	To keep your BMDS system current, check the BMDS website periodically for updates to the software or help manual.

CREATING A BMDS DESKTOP ICON

You may find it more convenient to run BMDS from a desktop shortcut icon. To do so:

1. Delete any older BMDS shortcut icons on your desktop.
2. In Windows Explorer, navigate to the newly installed BMDS application folder.
3. Right-click the BMDSxxx.exe file (where "xxx" denotes the current BMDS version number). A context menu appears.
4. Click Send To. A submenu appears.
5. Click "Desktop (Create Shortcut)". Windows creates a shortcut to the file on your desktop.

UNINSTALLING PREVIOUS VERSIONS OF BMDS

It is not necessary to uninstall previous versions of BMDS to install and run BMDS 2.6.0.1. However, to maintain the functionality of previous sessions, it is recommended that you retain the directory structure for the folders where your previous model runs reside.

The uninstall procedure depends on the version of BMDS you're running.

Uninstalling BMDS 2.1.2 and earlier

The uninstall process will ***NOT*** remove any data, option, session, output, or plot files you created in previous versions of BMDS.

1. Go to the Add/Remove Programs control panel (Windows XP or earlier) or the Programs and Features control panel (Windows Vista, Windows 7).
2. Select the BMDS program in the list.
3. Select Uninstall.

> ***Note*** If you don't have the required access rights in the computer, the **Remove** button will not be shown. You should uninstall BMDS by re-starting the original setup.exe file and then choosing "Remove Benchmark Dose Software."

TUTORIAL: RUNNING A BMDS SESSION

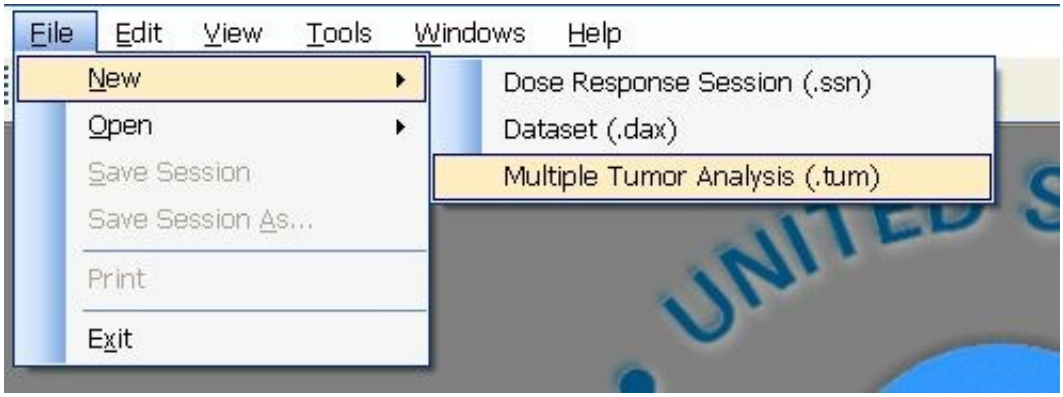
A BMDS session requires some initial setup. Once a session has been created and its parameters defined, it can be saved and run again later.

There are five primary steps for running a BMDS session, and each step has its own responsibilities and nuances. The following sections provide a simplified tutorial that overviews each step of the process. The tutorial also references more detailed procedural explanations located elsewhere in this documentation.

STEP 1: CREATE OR OPEN A SESSION FILE

Use the **File** menu commands or the BMDS toolbar to create a new session or open an existing session. The Session Grid window serves as the home base and organizing metaphor for your BMDS work, and you can use it to access other parts of BMDS, such as the Data Grid and Model Option Screen.

Creating a new session file

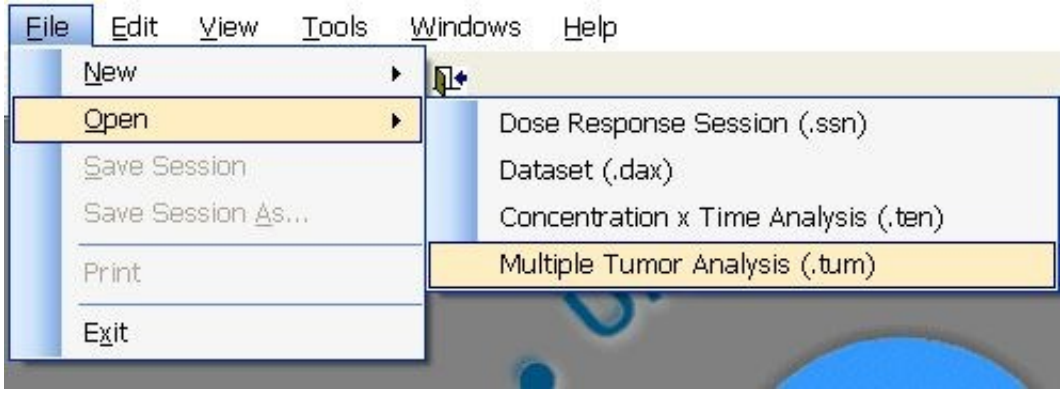


- Click the **New Session** button on the BMDS toolbar to open a new Session Grid window, or
- Use the **File>New** menu to select one of the options described in Table 1:

Table 1: *File>New menu options for creating a new session file*

Option	Description
Dose Response Session (.ssn)	Opens a new Session Grid window.
Multiple Tumor Analysis (.tum)	Creates a new session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis). You must specify data file and option file names to use for the session.

Opening an existing session



- Click the **Open Session** icon on the Toolbar, or
- Select the **File>Open>Dose Response Session (.ssn)** menu to display the Open dialog box and select a previously saved session (*.ssn) file.
- You can also select **File>Open>Concentration x Time Analysis (.ten)** to open a previously saved Concentration x Time Analysis (tenBerge) file or **File>Open>Multiple Tumor Analysis (.tum)** to open a previously saved session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis).

See also:

Working with the Session Grid

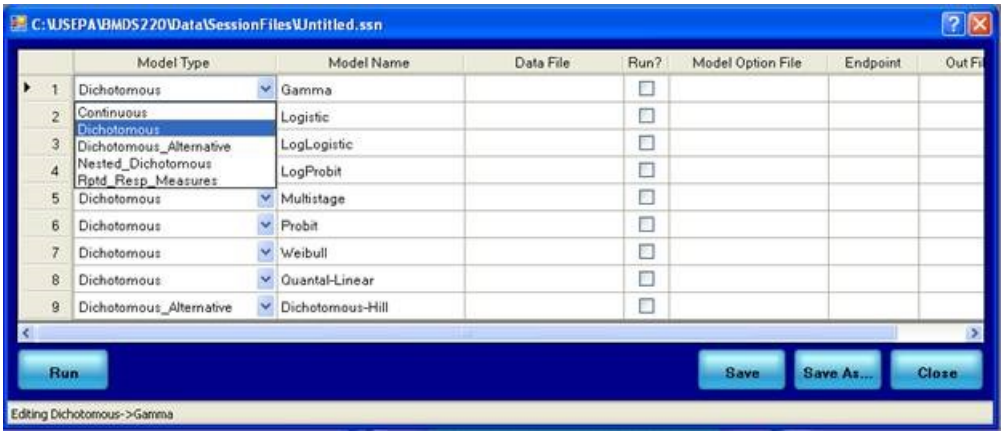
STEP 2: SELECT THE APPROPRIATE MODEL(S)

A BMDS session is typically used to analyze a single set of data with multiple models. However, BMDS is capable of processing multiple sets of data and multiple models in a single session.

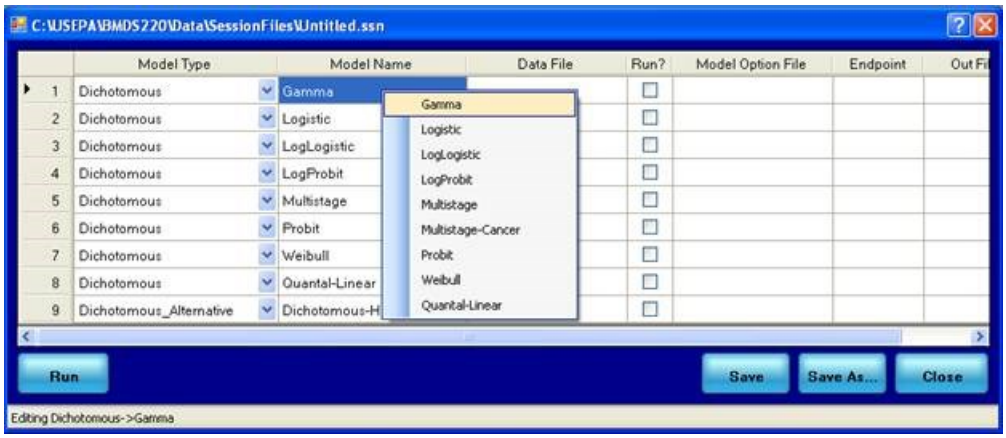
In this step, you use the BMDS Session Grid window to select the model(s) you want to run.

Selecting a Model Type and Model Name

1. With a session open and the session table displayed in the BMDS interface, use the drop down list in the Model Type column to select a model for that row.



2. Right-click in the row under the Model Name column to display a menu of appropriate models for the selected Model Type.



3. Click on the appropriate model name in the dropdown list to select it.

See also:

- Adding and Deleting Session Grid Rows
- Copying and Pasting a Data File Name
- Model Types and Abbreviations

STEP 3: CREATE OR IMPORT A DATASET

Data are stored in files with the *.dax extension. You can use commands from the Session Grid window to call up the Data Grid window, which you use to enter

and edit data. After the data are entered/modified as desired, you can save and close the Data Grid window.

The file name that appears in the Session Grid's Data File column should be the same file name that appears in the Data Grid window's title bar.

Working with data files

If a session or dataset is already loaded in the Session Grid window, right-click on a field in the Data File column to display a context menu of options.

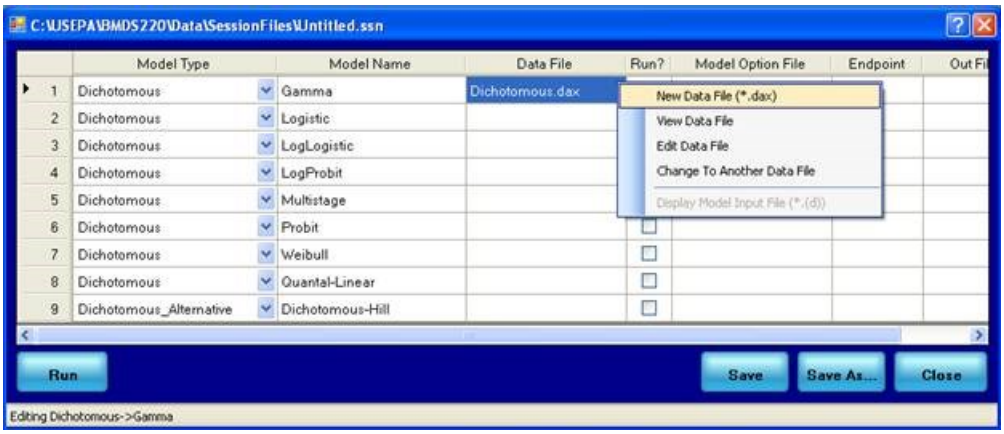


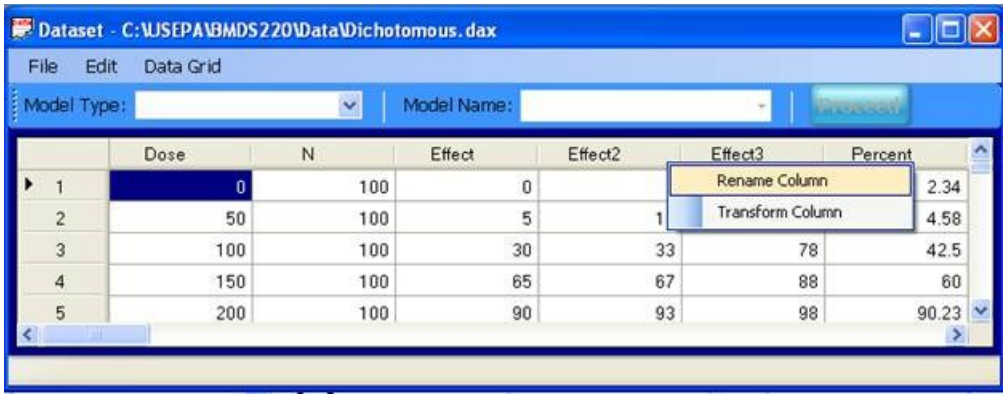
Table 2 describes the available context menu options.

Table 2: *Context menu options for data files*

Option	Description
New Data File (*.dax)	Create a new data file using the Data Grid window
View Data File	View the currently selected data file in a read-only Data Grid window
Edit Data File	Edit the currently selected data file in the Data Grid window
Change to Another Data File	Display the Open dialog box to select a different data file

Working with the Data Grid window

Right click on the column titles to display column options. You can rename a column or create a new column of data by running a mathematical operation on the existing data.



For the BMDS-provided session templates, the data grid contains pre-specified column labels depending on the Model Type. The column labels for each model type are described in Table 3.

Table 3: *Pre-specified column labels for each model type*

Model Type	Pre-Specified Column Labels
Dichotomous	Dose, N, Effect
Nested	Dose, Response, Total, Litter
Continuous	Dose, N, Mean, Std
Cancer	Dose, N, Effect, Effect2, Effect3, Percent

Selecting a Model and Adding Data

With the Data Grid open, you can select the Model Type and Modelyou want to run on the dataset. Afterward, you can choose to open an existing dataset or manually enter or import data. Using the standard Windows Cut-Copy-Paste commands, you can also copy and paste data from an Excel spreadsheet into the Data Grid.

See also:

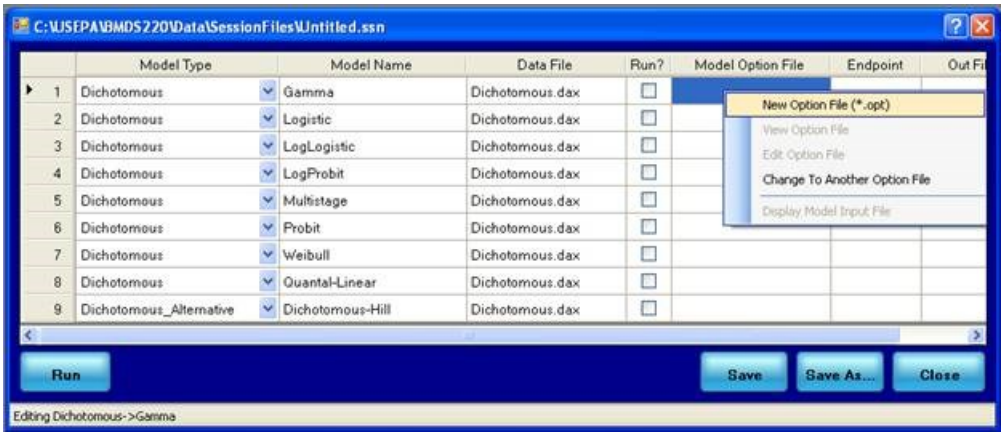
- Working with the Data Grid and Datasets
- Working with the Session Grid
- Using Session and Option File Templates
- Copying and Pasting a Data File Name

STEP 4: SPECIFY MODEL PARAMETERS

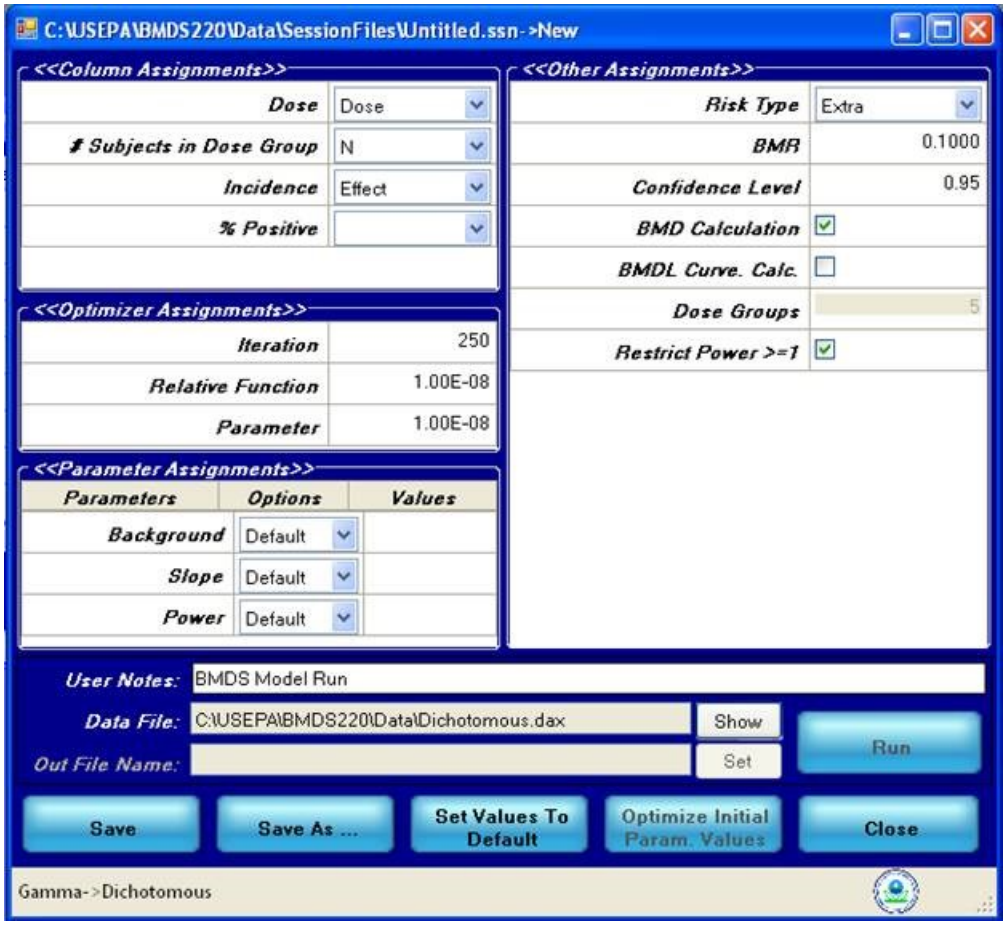
After selecting the model (in the Session Grid) and creating or importing the dataset (in the Data Grid), the next step is to specify the parameters associated with the model. You can do this by choosing or creating a new option file.

Creating a new model options file

A model's option parameters are stored in files with the *.opt extension. In the Session Grid, right-click on a field under the Model Option File column to display menu options enabling you to create a new option file or select an existing option file.



Selecting the **New Option File (*.opt)** command displays the Model Option Screen, shown below. From this screen, you can view and edit the parameter options.



After specifying the parameters, press the **Save** or **Save As …**buttons to save your work in an option file. Option files may be saved to a specified path, set to default values, and optimized using the buttons along the bottom of the window.

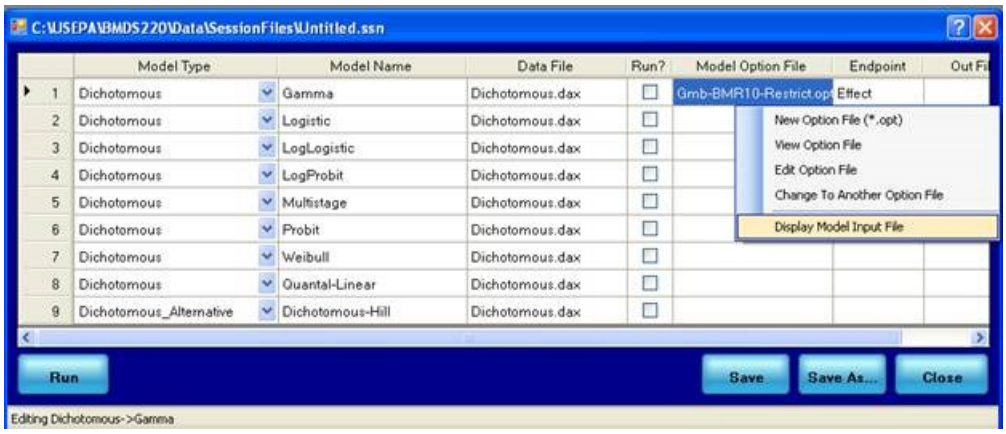
The Model Option Screen's status bar displays the model and model type that the parameters will affect. In the previous screenshot, the selected model is Dichotomous and the model type is Gamma.

Enter any freestyle text into the **User Notes** field to capture important information about the parameters.

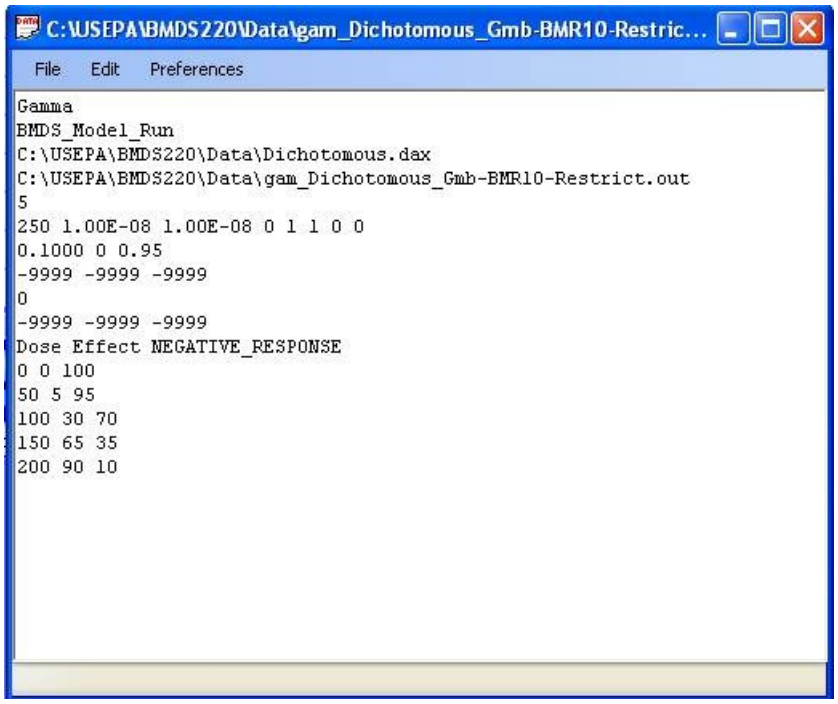
The data file that will be used (and its path) are displayed in the **Data File** field. Click the **Show** button to display the file's contents in the Data Grid window.

Displaying the Model Input File

After an option has been created or added to the session, right-click on the option file's name and select **Display Model Input File** from the session screen to view the model input file. The model input file's format is *.d.



The following screenshot shows the model input file as displayed within the BMDS text viewer. Within this viewer you can edit, save, or print the model input file.



See also:

- Working with the Model Option Screen
- Working with the Model Option File Column

STEP 5: RUN THE MODEL AND VIEW RESULTS

After you have specified the session, model, dataset, and model parameters, BMDS is ready to run the model.

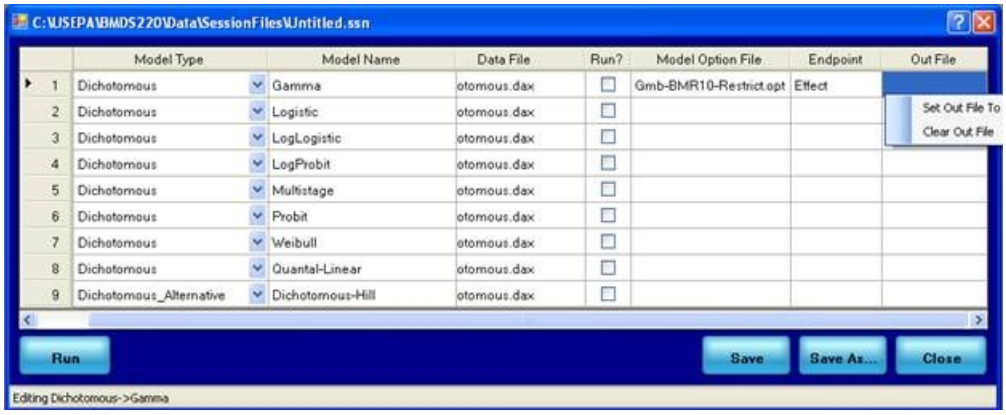
Specifying output file names

BMDS automatically assigns an output file name for each model run (session row) corresponding to the following naming convention:

```
[3 letter model abbreviation]-[name of data file]-[name of option file].out
```

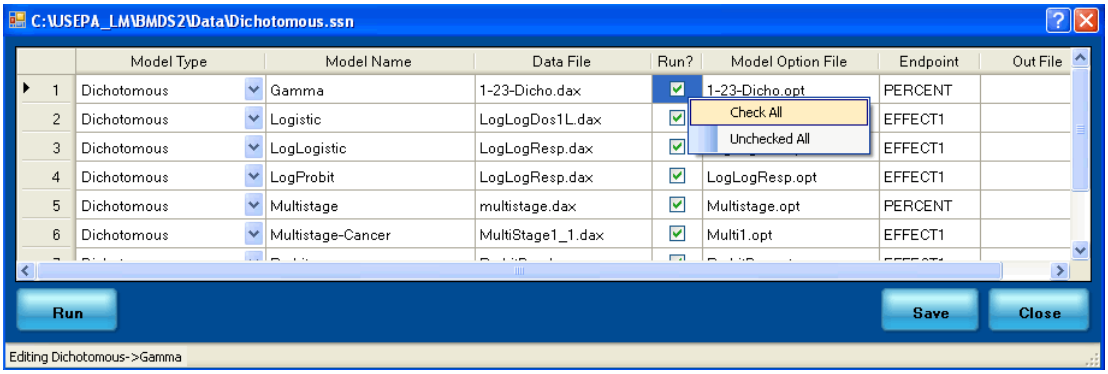
Model abbreviations are listed here.

If you want to use a different output file name, right-click in a specific **Out File** column cell to specify a file name that will contain the result output.



Selecting which models to run

Select which models to run by placing checkmarks in the appropriate rows under the **Run?** column. Right clicking will display a submenu allowing all boxes to be checked or unchecked at once.

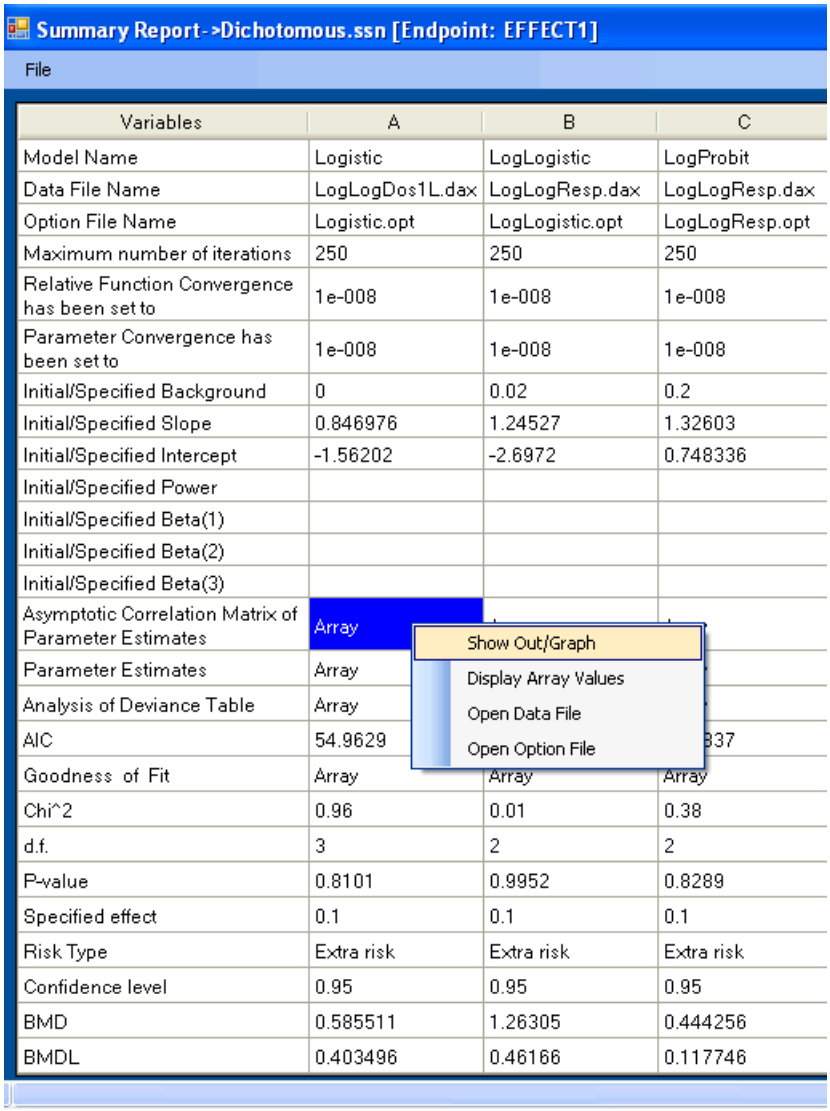


After you have selected the models to be run in the session, click the **Run** button in the bottom left of the Session Grid window. The Session Grid's status bar will display a “Please wait processing . . .” message while BMDS calculates the results.

Viewing the results

If the "Summary Report" option has been selected under the **Tools > Options** menu, the results will be displayed in two new windows: a textual Summary Report and a Summary Graph.

The Summary Report window displays the variables set for each of the models run in a tabular format. Each lettered column corresponds to the models previously added in the session window.



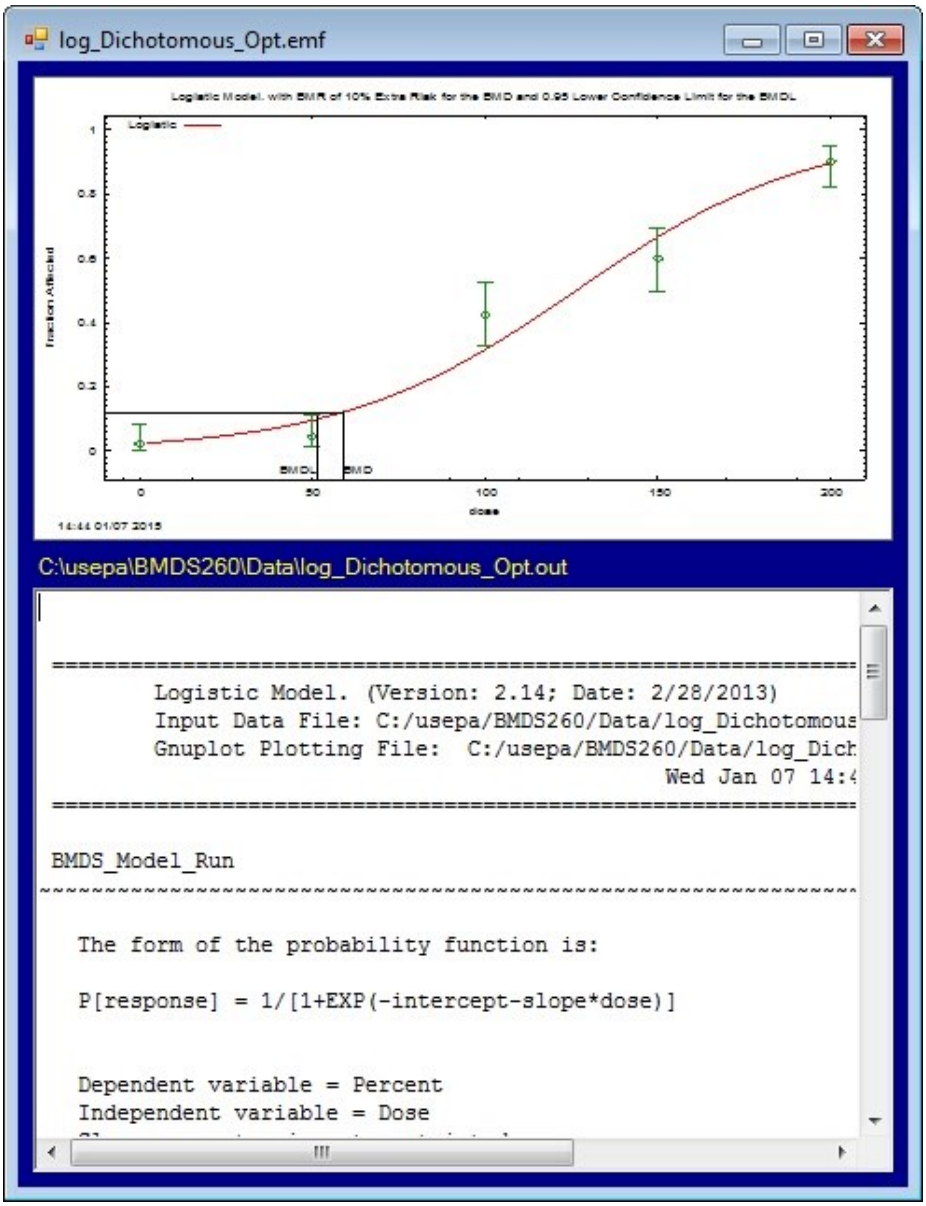
Variables	A	B	C
Model Name	Logistic	LogLogistic	LogProbit
Data File Name	LogLogDos1L.dax	LogLogResp.dax	LogLogResp.dax
Option File Name	Logistic.opt	LogLogistic.opt	LogLogResp.opt
Maximum number of iterations	250	250	250
Relative Function Convergence has been set to	1e-008	1e-008	1e-008
Parameter Convergence has been set to	1e-008	1e-008	1e-008
Initial/Specified Background	0	0.02	0.2
Initial/Specified Slope	0.846976	1.24527	1.32603
Initial/Specified Intercept	-1.56202	-2.6972	0.748336
Initial/Specified Power			
Initial/Specified Beta(1)			
Initial/Specified Beta(2)			
Initial/Specified Beta(3)			
Asymptotic Correlation Matrix of Parameter Estimates	Array		
Parameter Estimates	Array		
Analysis of Deviance Table	Array		
AIC	54.9629		337
Goodness of Fit	Array	Array	Array
Chi^2	0.96	0.01	0.38
d.f.	3	2	2
P-value	0.8101	0.9952	0.8289
Specified effect	0.1	0.1	0.1
Risk Type	Extra risk	Extra risk	Extra risk
Confidence level	0.95	0.95	0.95
BMD	0.585511	1.26305	0.444256
BMDL	0.403496	0.46166	0.117746

Right-click in any lettered column to display a menu with the options described in Table 4.

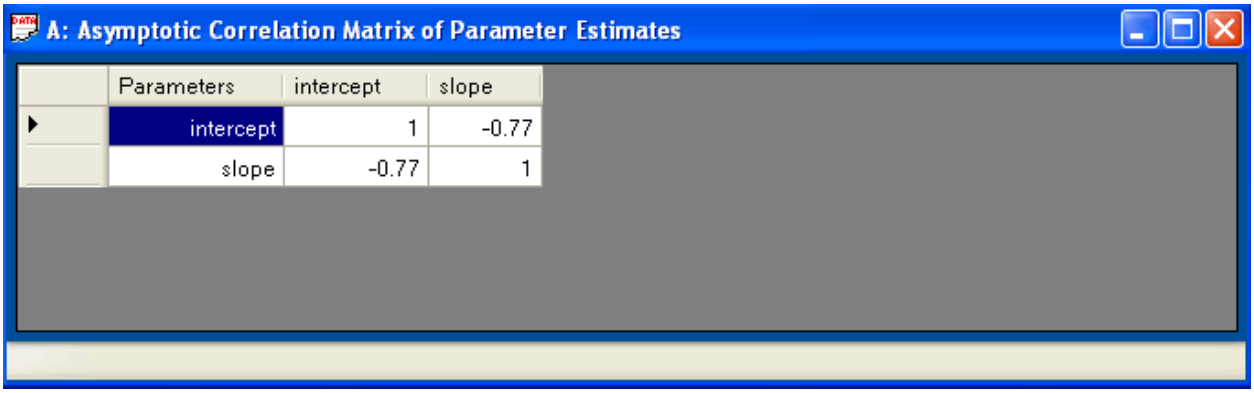
Table 4: *Summary Report window's context menu options*

Option	Description
Show Out/Graph	Display individual graphs and Out File data
Display Array Values	To display array values, right-click on a cell containing the word "Array."
Open Data File	Display the data file linked to the displayed results.
Open Option File	Display the option file linked to the displayed results.

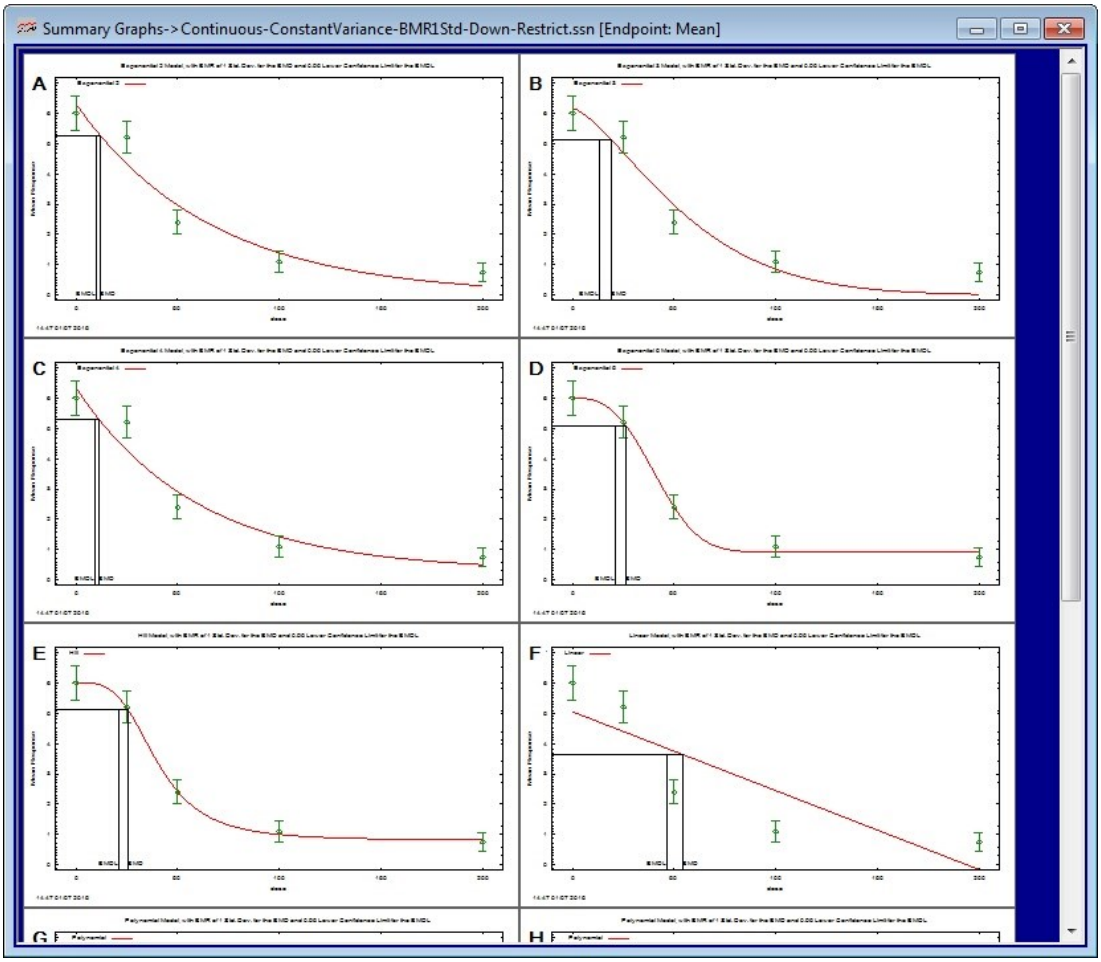
The following screenshot shows an example of an individual graph and Out File data display.



Display array data by selecting **Display Array Values** from the Summary Report window. The following screenshot displays the result.



The Summary Graphs window displays graphs corresponding to each model run. Individual graphs may be copied to the clipboard and inserted into other files such as Microsoft Word documents.



See Also:

- Working with Reports and Output
- Viewing Output Files
- Viewing Plots
- Using GnuPlot

WORKING WITH THE MENUS, TOOL BARS, & STATUS BARS

At all times, BMDS displays a menu bar and a tool bar at the top of the BMDS application window, and a status bar at the bottom of the window.

BMDS presents different menu options depending on the type of window displayed, such as the Session window. The Data Grid window, which opens within the BMDS main window, presents a reduced set of menu options.

This section describes the different options provided by the BMDS menus and toolbar. It also describes the information conveyed by the status bar.

FILE MENU

Table 5: *File menu options*

Command	Function
New/Dose Response Session (.ssn)	Creates a new session

New/Dataset (.dax)	Creates a new dataset with a default extension of .dax.
	Selecting this item displays a submenu with the following options:
	• Continuous Data. Selecting this item displays another submenu, with the following options:
	  • Summarized (Means & Stds)
	  • Individual Response
	• Dichotomous Data
	• Nested Data
	• Generic Data

New/Multiple Tumor Analysis (.tum)	Creates a new session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis).
Open/Dose Response Session (.ssn)	Opens previously saved session.
Open/Dataset (.dax)	Opens previously saved dataset.
Open/Concentration x Time Analysis (.ten)	Opens previously saved Concentration x Time Analysis (tenBerge) file.
Open/Multiple Tumor Analysis (.tum)	Opens previously saved session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis).
Save Session (Session window)	Saves changes to the selected session.
Save Session As … (Session window)	Displays the standard Windows Save As dialog box so the current session can be saved under a new filename.
Close Session (Session window)	Closes the selected Session window.

Command	Function
Print	Prints the contents of the selected Session window.
Exit	Closes the BMDS application. BMDS will prompt you to save any unsaved changes.
Print Setup (Session window)	Displays the standard Windows Print Setup dialog box, where you can select such options as orientation, margins, paper size, and so on.
Print Preview (Session window)	Displays a new window showing how the printed document will look. The toolbar buttons at the top of the window enable you to display one or more pages at a time, change magnification, jump to a specific page, and so on.

EDIT MENU

The Edit menu commands assist with copying, cutting and pasting data within the BMDS output file. The commands can be implemented by selecting them from the menu with a mouse or by using the indicated key strokes.

Table 6: *Edit menu options*

Command	Function
Cut (Ctrl+X)	Selected data is cut from an active output file.
Copy (Ctrl+C)	Selected data is copied from an active output file; or a selected data file name is copied from the Data File column of an active session grid.
Paste (Ctrl+V)	Cut/copied data is pasted into output file at cursor location.
Delete (Del)	Delete selected data.
Select All (Ctrl+A)	Selects all text in current active window.

VIEW MENU

Table 7: *View menu options*

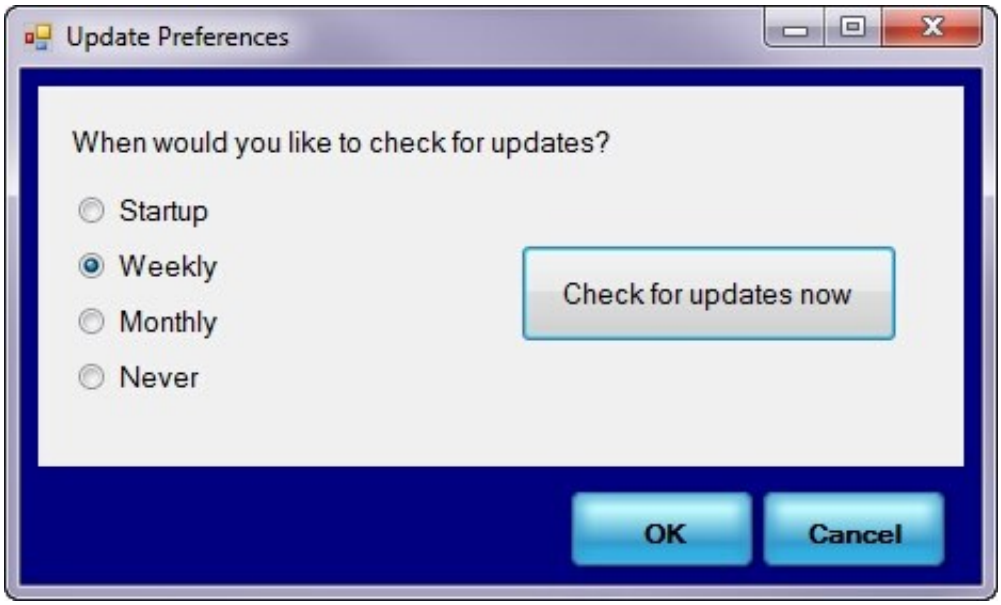
Command	Function
Tool Bar	Toggles the visibility of the tool bar and icons. A checkmark to the left of this option in the menu indicates the tool bar is visible.
Status Bar	Toggles the visibility of the status bar at the bottom of the BDMS screen. A checkmark to the left of this option in the menu indicates the status bar is visible.

TOOLS MENU

Table 8: *Tools menu options*

Command	Function
View Plot …	Displays a submenu for the following options to use for viewing a graph: • Using BMDS … • Using GnuPlot …
View Output File …	Opens saved Output file in new window.
Preferences …	Displays separate Preferences dialog boxes for the Update function, Summary Report windows, and Data Grid windows.

BMDS displays the following dialog box for Update Preferences:



Select how often or whether you want BMDS to check for new versions of the software. Click **Check for updates now** to manually check for BMDS updates. BMDS will display a message stating either that the current version is up to date or that a new version is available for download and install.

BMDS displays the following dialog box for Report Preferences:

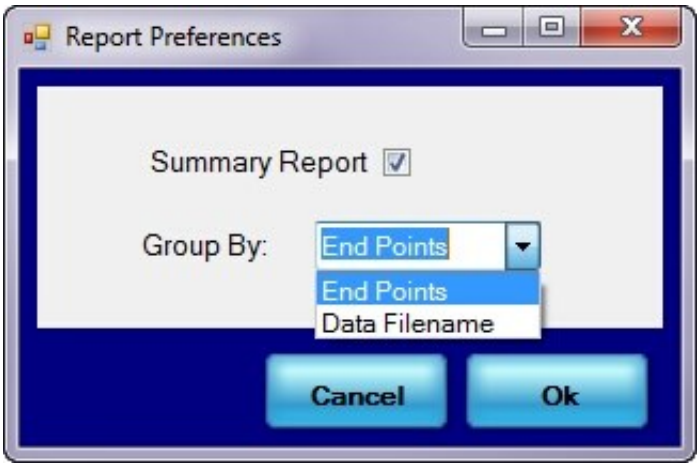


Table 9: *Report Preferences options*

Option	Function
Summary Report	A checkmark to the right of this option indicates a summary report and summary plots will be displayed after a session run. If unchecked, the summary report is not generated and plots are displayed in separate windows.
Group By	This option determines how a session's results (summary reports and summary plots) are grouped together. Results can be grouped by end points or by the data filename.

BMDS displays the following dialog box for Data Grid preferences:

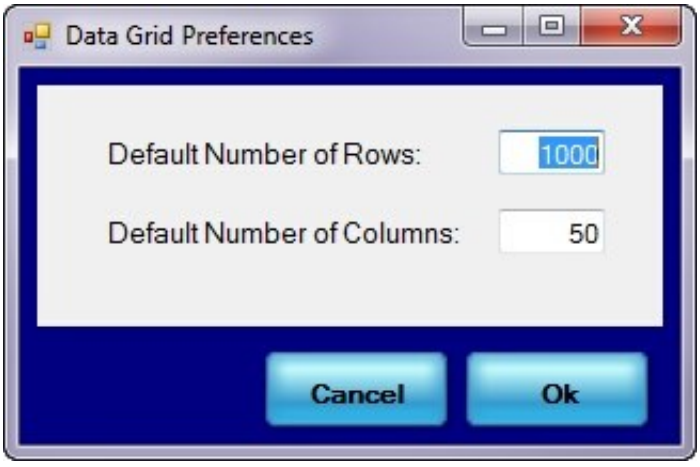


Table 10: *Data Grid Preferences options*

Option	Function
Default Number of Rows	Determines how many rows appear when creating a new dataset.

Option	Function
Default Number of Columns	Determines how many columns appear when creating a new dataset.

Session Grid menu

This menu is available only when a session window is open.

Table 11: *Session Grid menu options*

Command	Function
Insert Row	Inserts a new row above the currently selected row in the session grid. The currently selected row is indicated by the black arrow to the left of the row number.
Add Row(s)	From the dropdown list, select a predefined number of rows to add to the session grid or all the models of a chosen group to add. BMDS creates the rows only after Add Row(s) is selected.
Delete Row	Deletes the currently selected row in the session grid.

Data Grid menu

This menu is available only when a Data Grid window is open.

Table 12: *Data Grid menu options*

Command	Function
Add Column(s)	From the dropdown list, select a predefined number of columns to add to the data grid. BMDS creates the columns only after Add Column(s) is selected.
Add Row(s)	From the dropdown list, select a predefined number of rows to add to the data grid. BMDS creates the rows only after Add Row(s) is selected.
Insert Row	Inserts a new row above the currently selected row in the data grid. The currently selected row is indicated by the black arrow to the left of the row number.
Insert Column	Inserts a new column to the left of the current column. The column that has a selected cell is the current column.
Delete Row	Deletes the currently selected row in the data grid.
Delete Column	Deletes the currently selected column in the data grid. The column that has a selected cell is the current column.

Windows Menu

Options under the Windows menu are only available when multiple windows are open inside the BDMS program.

Table 13: *Windows menu options*

Command	Function
Tile Horizontal	Tiles windows horizontally.
Tile Vertical	Tiles windows vertically.
Cascade	Displays windows in a cascade arrangement.
Close all	Closes all windows inside the BDMS program.
Window List	A list of currently open windows is displayed. Clicking on a particular window name will bring the selected window to the top. The current top window will have a checkmark to the left of its name.

Help Menu

Table 14: *Help menu options*

Command	Function
BMDS Help	Displays the contents of the Help documentation in a new window.
Quick Start	Opens the BMDS Quick Start Guide in the default web browser.
BMD Technical Guidance	Opens the BMD Technical Guidance PDF in the default web browser.
BMDS Home	Opens the BMDS Home page in the default web browser.
BMDS Support	Currently not implemented.
About …	Window describing the BMDS Sponsors and Credits, BMDS program version, and a disclaimer.

Tool Bar

Table 15: *Tool Bar buttons and options*

Icon	Command	Function
	**New**	Creates a new session window.
	**Open**	Opens a previously saved session. A regular Dose-Response session (a file with the .ssn extension) or an existing Concentration x Time model analysis (a file with the .ten extension) may be opened this way.

Icon	Command	Function
	**Save Session**	Saves the current session.
	**Print**	Prints the results of the current session.
	**New Dataset**	Create a new dataset.
	**Open Dataset**	Opens an existing dataset.
	**View Output File**	Opens saved Output file in new window.
	**Exit**	Exit the program.

Status Bar

Each window in BMDS has its own status bar and communicates different information.

Table 16: *Status bar information for BMDS windows*

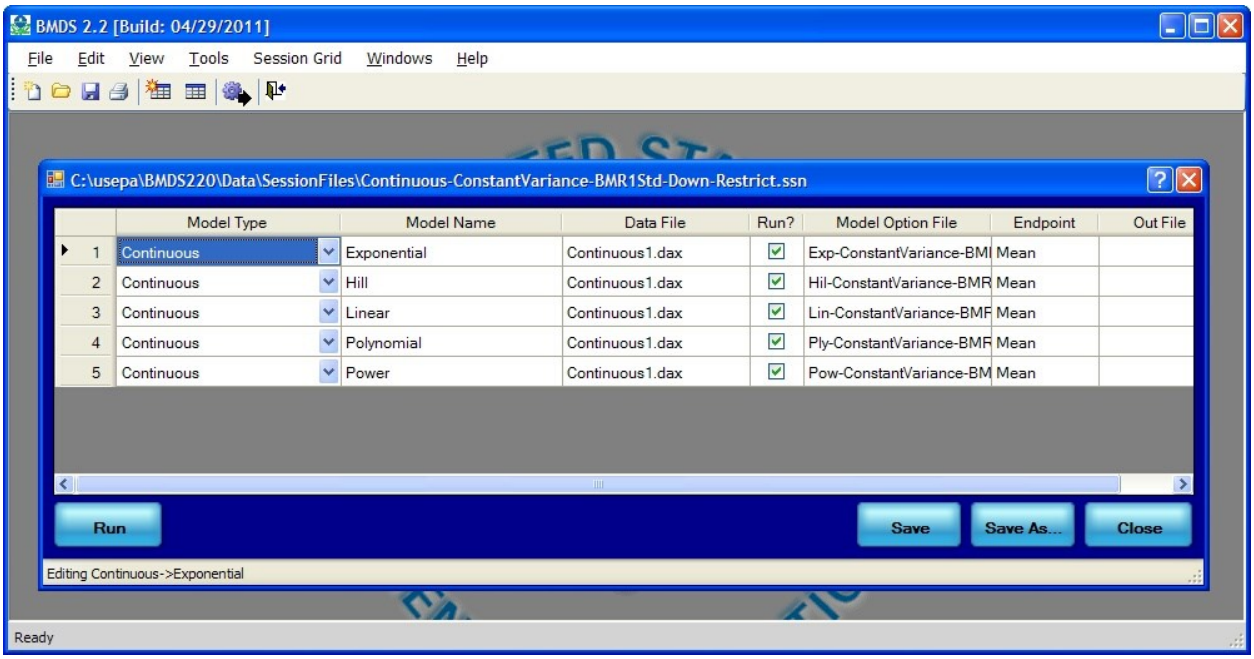
Status Bar Location	Functions
BMDS application window	Displays the results of actions executed within session and data windows, such as when rows or columns are inserted, a session is saved, or when a parameter options file is opened for editing.
Session Grid	Displays the Model Type and Model Name for the currently selected row.
Parameter Options window	Displays the Model Type and Model Name for the currently selected row.

WORKING WITH THE SESSION GRID

From the Session Grid window, you can specify the models you want to use and run one or more sessions at a time. The Session Grid also enables you to drill down to data files, option files, and parameter settings for a specific session.

THE SESSION GRID WINDOW

The Session Grid window opens inside the BMDS application, as shown in the following screenshot.



Components of the BMDS application window are, from top to bottom:

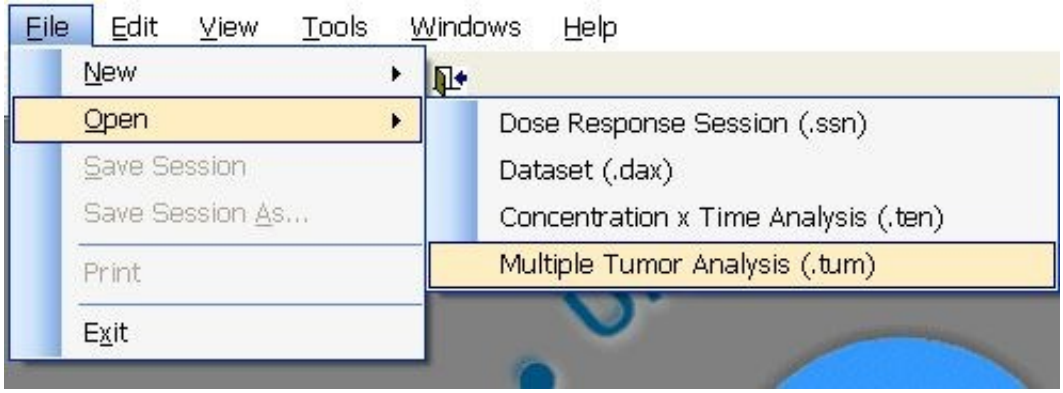
- BMDS title bar with the current BMDS version number.
- The BMDS menu bar. When a session window is open, the **Session Grid** menu appears.
- The BMDS toolbar.
- At the bottom of the window is the BMDS status bar.

Components of the Session Grid window are, from top to bottom:

- The Session Grid title bar displays the path and file name of the currently loaded session file.
- Rows and columns arranged as in a spreadsheet. From the dropdown lists, you can specify the models you want to run for a session.
- Buttons to run or save a session and to close the Session Grid window.

OPENING EXISTING SESSION FILES

- Click the **Open Session** icon on the Toolbar, or
- Select the **File>Open>Dose Response Session (.ssn)** menu to display the Open dialog box and select a previously saved session (*.ssn) file.
- You can also select **File>Open>Concentration x Time Analysis (.ten)** to open a previously saved Concentration x Time Analysis (tenBerge) file or **File>Open>Multiple Tumor Analysis (.tum)** to open a previously saved session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis), as shown in the following screenshot.



CREATING A NEW SESSION FILE

- Click the **New Session** button on the BMDS toolbar to open a new Session Grid window, or
- Use the **File>New** menu to select one of the options described in Table 17.

Table 17: *Menu options for creating a new session grid*

Options	Description
Dose Response Session (.ssn)	Opens a new Session Grid window.
Multiple Tumor Analysis (.tum)	Creates a new session for the analysis of multiple tumors via multistage modeling (Multiple Tumor Analysis). You must specify data file and option file names to use for the session.

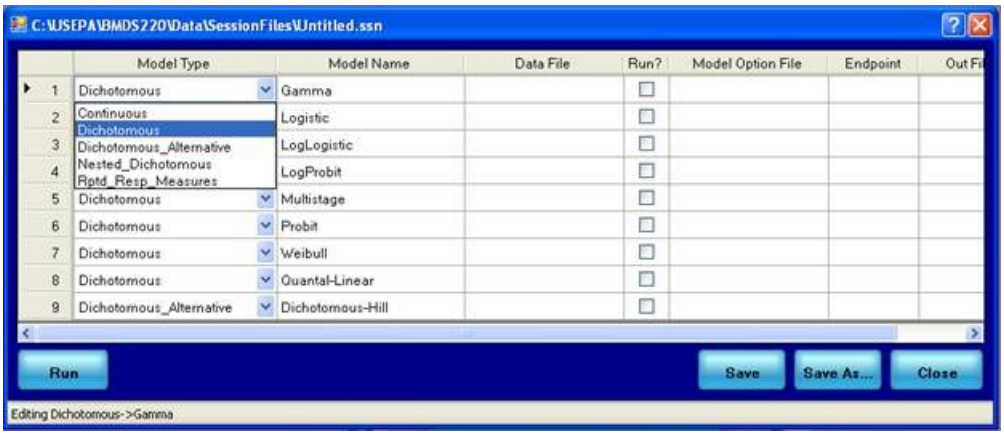
See also:

- Working with the Session Grid
- Working with the Data Grid and Datasets

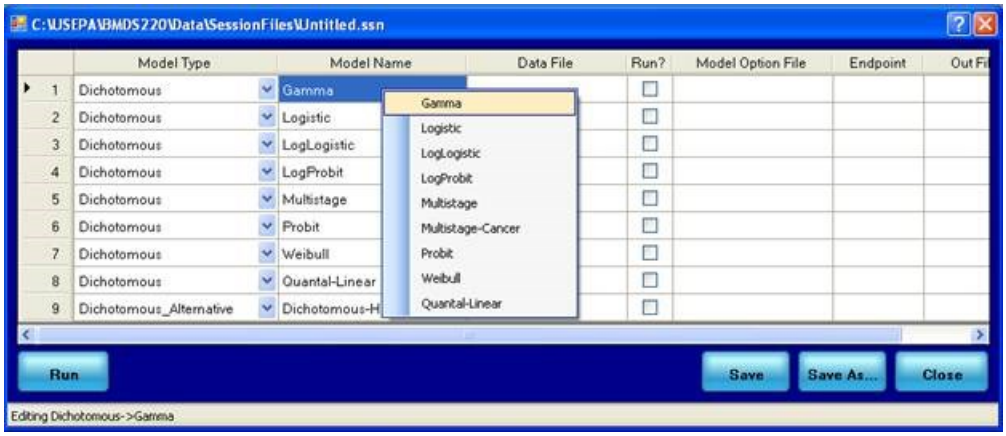
SELECTING THE APPROPRIATE MODEL(S) FOR THE DATA

A BMDS session is typically used to analyze a single set of data with multiple models. However, BMDS is capable of processing multiple sets of data and multiple models in a single session.

1. With a session open and the session table displayed in the BMDS interface, use the drop down list in the Model Type column to select a model for that row.



2. Right-click in the row under the Model Name column to display a menu of appropriate models for the selected Model Type.



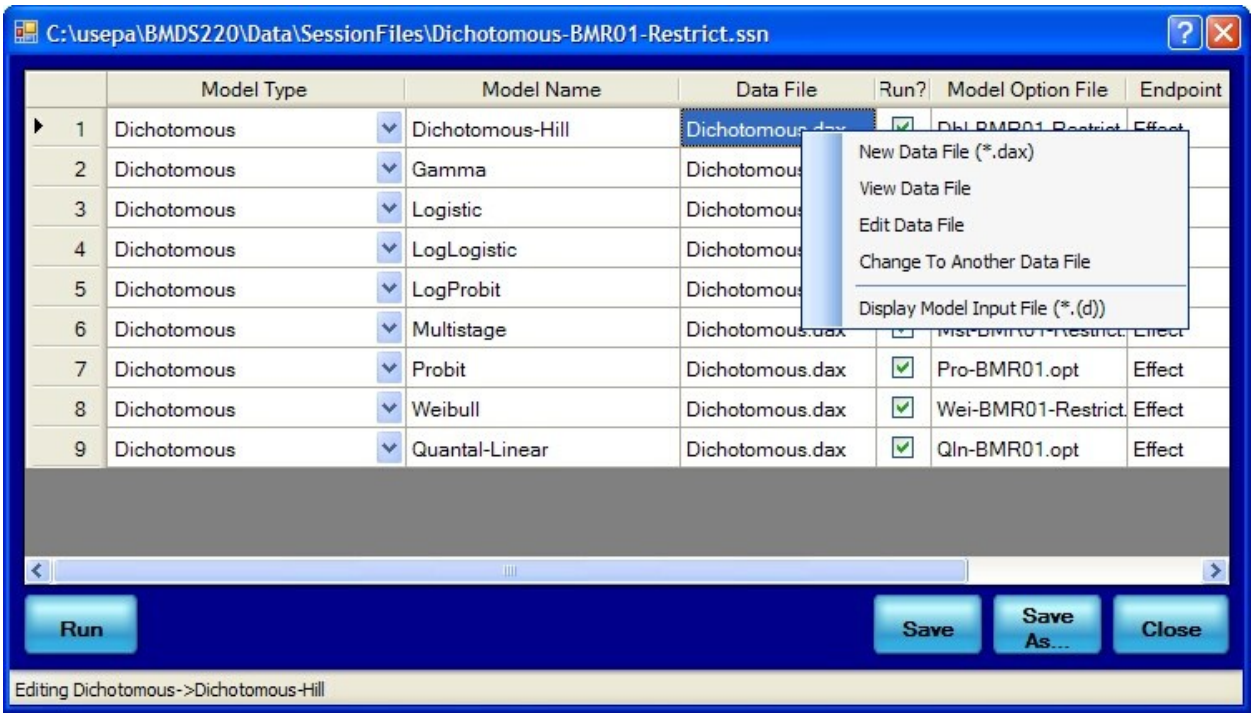
3. Click on the appropriate model name in the dropdown list to select it.

See also:

- Adding and Deleting Session Grid Rows
- Copying and Pasting a Data File Name
- Model Types and Abbreviations

WORKING WITH THE DATA FILE COLUMN

From the Session Grid, you can open the Data Grid window to create a new dataset, switch to a different dataset, or edit or view an existing dataset. You can also open the Model Input File, which is a text file that contains instructions for running the model.



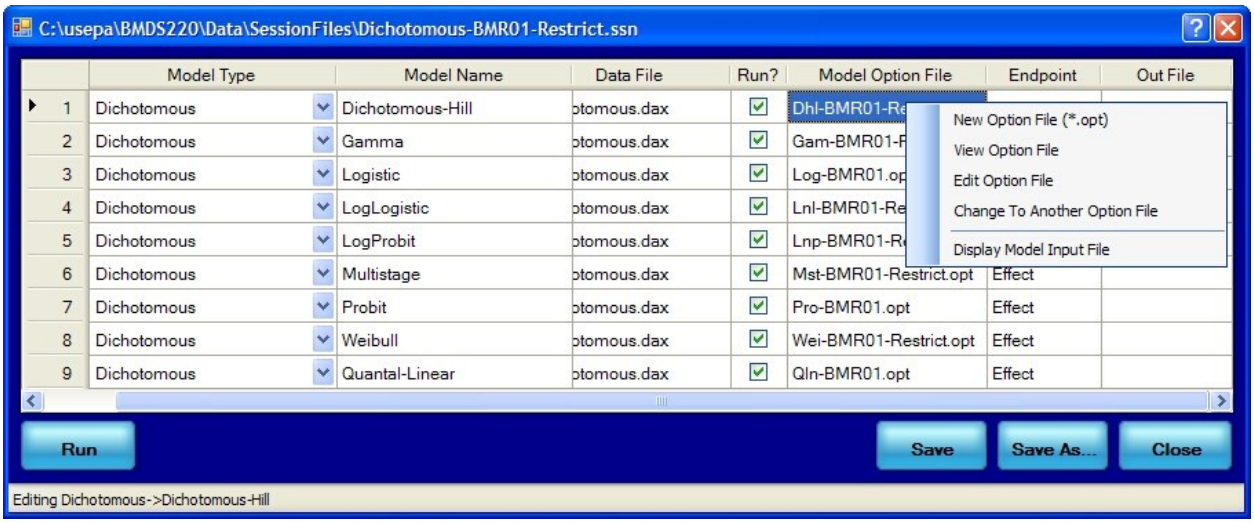
With a session open in the Session Grid and with datasets specified in the Data File grid, you can right-click on any Data File column cell and select options described in Table 18.

Table 18: *Data File column's context menu options*

Command	Action
New Data File (*.dax)	Opens an empty, untitled dataset ("UntitledData.dax") in a new Data Grid window.
View Data File	Opens the selected dataset into a read-only Data Grid window. You cannot modify data in this view.
Edit Data File	Opens the selected dataset into a new Data Grid window for editing.
Change to Another Data File	Displays an Open dialog box where you can select a different data file to be used for that model.
Display Model Input File (*.(d))	Opens a text-edit window within BMDS that displays the model input file. You can view, modify, and save the model's input parameters from the text-edit window.

WORKING WITH THE MODEL OPTION FILE COLUMN

From the Session Grid, you can open the Model Option Screen to create a new option file, select a different option file, or edit or view the selected option file. You can also open the Model Input File, which is a text file that contains instructions for running the model.



With a session open in the Session Grid and with option files specified in the Data File grid, you can right-click on any Model Option File column cell and select the context menu options described in Table 19.

Table 19: *Model Option File column's context menu options*

Command	Action
New Option File (*.opt)	Opens a new Model Option screen for the selected model type.
View Option File	Opens the selected option file into a read-only Model Option screen. You cannot modify data in this view.
Edit Option File	Opens the selected option file into a new Model Option Screen for editing.
Change to Another Option File	Displays an Open dialog box where you can select a different option file to be used for that model. The default is the BMDS OptionFiles directory.
Display Model Input File	Opens a text-edit window within BMDS that displays the model input file. You can view, modify, and save the model's input parameters from the text-edit window.

> ***Note*** When working within a session, changes made to one option file (i.e., for one model) can be "transferred" to other option files included in that session (i.e., those for other models). Changes to the dose, sample size, response, mean, or standard deviation variables can therefore be done without having to make those changes separately in every option file. The user will be prompted to choose whether variable name assignment changes made in one option file should be made in all other option files included in that session.

See also:

Working with the Model Option Screen

WORKING WITH THE OUT FILE COLUMN

The results of a BMDS session run are saved to an output file (*.out).

BMDS automatically assigns an output file name for each model run (session row) corresponding to the following naming convention:

```
[3 letter model abbreviation]-[name of data file]-[name of option file].out
```

An example output file name would be:

```
lin_Continuous2_Lin-ConstantVariance-BMR1Std-IndResp.out
```

Clearing the current output file name

1. Select a cell in the Session Grid's Out File column that has an output file name.
2. Right-click to display the popup menu and select **Clear Out File**. The cell's contents are cleared.

Specifying a new output file name

1. Select a cell in the Session Grid's Out File column. The cell can be empty or contain an output file name.
2. Right-click to display the popup menu and select **Set Out File To**. The Save As dialog is displayed. Select the file you want to use or enter the name of the file as you want it to appear in the Out File column.

See also:

- Step 5: Run the Model and View Results

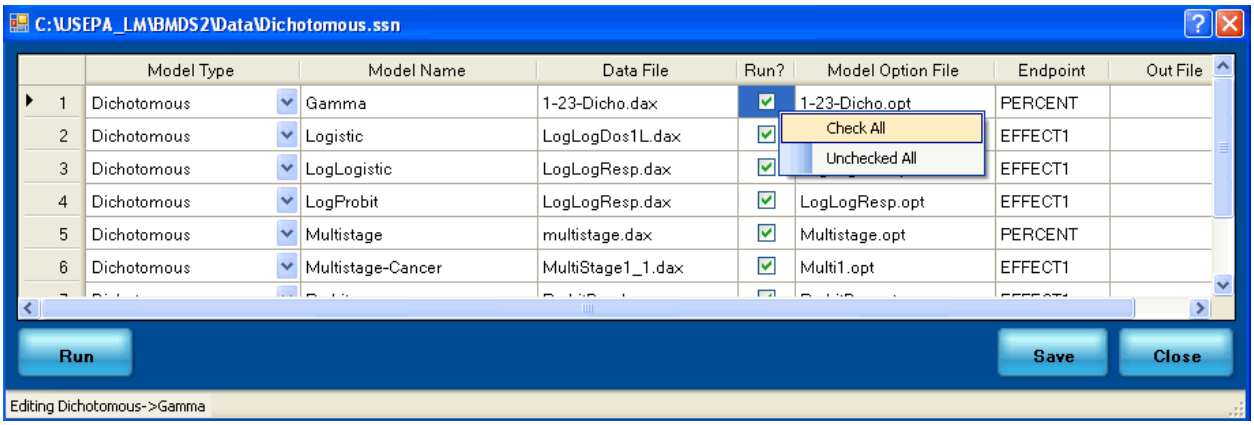
- Model Types and Abbreviations

SPECIFYING THE MODELS TO INCLUDE IN A SESSION

After you have defined the models, data, parameters, and output file names, you must select which models to be included in the session run.

Placing checkmarks in the appropriate rows under the **Run?** column will include those models in the session run.

Right clicking will display a submenu allowing all boxes to be checked or unchecked at once.



After you have selected the models to be included in the session run, click the **Run** button in the bottom left of the Session Grid window.

See also:

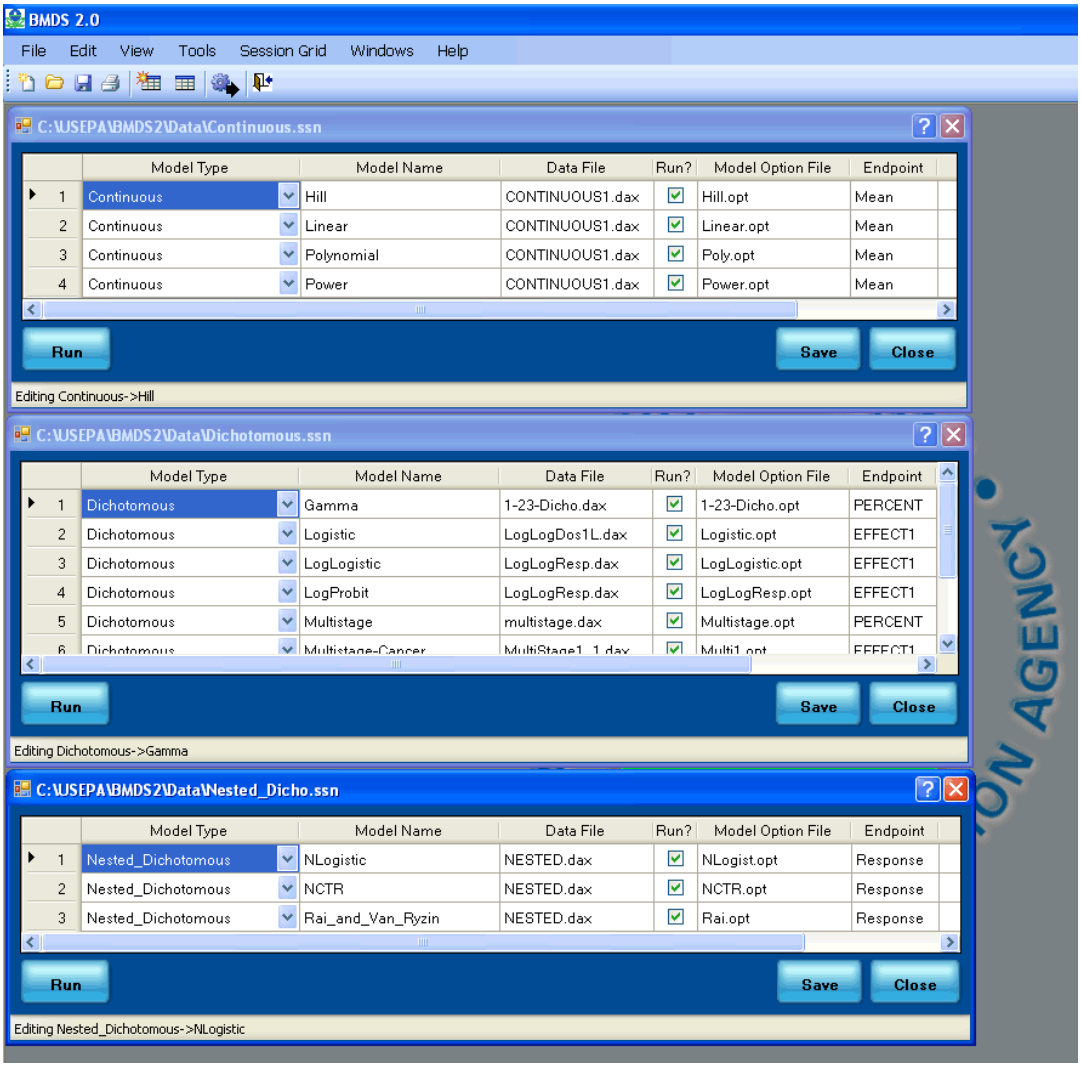
Step 5: Run the Model and View Results

RUNNING MULTIPLE SESSIONS

In addition to running a session, BMDS can run multiple sessions simultaneously. That is, BMDS can compute the results of a session while running computations on a separate session.

To run multiple sessions, open and specify more than one Session Grid window and click each window's **Run** button.

The following screenshot shows three separate Session Grid windows open within the BMDS application window.



ADDING AND DELETING SESSION GRID ROWS

You can add columns and rows to, and delete rows from, Session Grids and Data Grids.

You can delete columns from Data Grids only.

> ***Note*** When all of the cells in a column/row are empty the column/row is removed when the dataset is saved. However, if a column/row contains any data at all, the column/row is retained when the dataset is saved.

- To insert a row above the currently selected row, select **Session Grid>Insert Row**.
- To delete the currently selected row, select **Session Grid>Delete Row**.

- To add multiple rows above the currently selected row, select **Session Grid**, pick a pre-defined option from the dropdown list, and click **Add Row(s)**.

  You can add either a number of rows (1, 2, 5, 10, or 20) before the currently selected row or all the models for a selected Model Type (All Continuous, All Dichotomous, All Dichotomous Alternative, All Nested Dichotomous). Adding All Continuous, for example, inserts 5 rows of the Continuous model type, with each continuous model in its own row (Exponential, Hill, Linear, Polynomial, and Power).

See also:

- Working with the Menus, Tool Bars, & Status Bars
- Adding and Deleting Data Grid Columns and Rows

COPYING AND PASTING A DATA FILE NAME

1. In a Session Grid, click on a filename in the Data File column.
2. Press Ctrl-C or select **Edit>Copy** to copy the data file reference.
3. Click on a blank cell in the Data File column where you want to insert the reference.
4. Press Ctrl-V or select **Edit>Paste**.

See also:

Copying, Cutting, and Pasting Data

WORKING WITH THE DATA GRID AND DATASETS

Data are stored in files with the *.dax extension, but you can import files of other formats (space-, tab-, or comma-delimited, Excel 2003, or BMDS 1.xx).

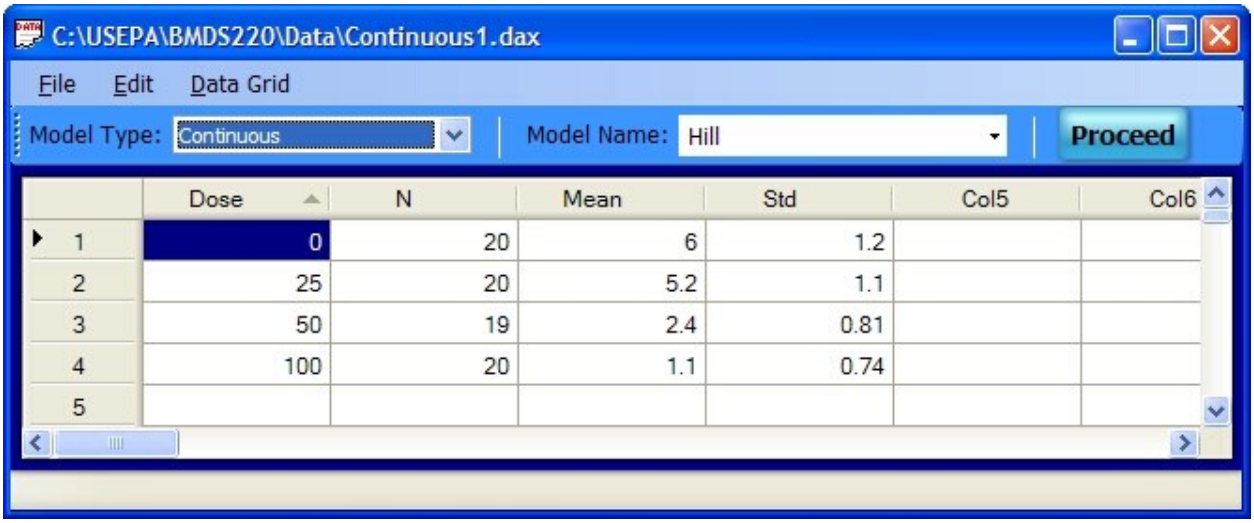
Use the Data Grid window to enter and edit data. After the data are entered/modified as desired, you can save and close the Data Grid window. The appropriate data file name should be displayed in the Session Grid's Data File column.

The default number of rows and columns for a new Data Grid window is 1000 and 50, respectively, but you can change this in the **Tools>Preferences** menu.

Note **Decimal Separators:** BMDS supports regional settings for the decimal separator in the user interface and in spreadsheets created by the Export to Excel function.

Thousands Separators: No “thousands separator” (regardless of regional setting) can be used in the data; that is, one thousand can only be written as 1000 rather than as 1,000.

THE DATA GRID WINDOW



Components of the Data Grid window are, from top to bottom:

- The title bar, which includes the path and file name of the currently loaded dataset.
- The menu bar, with its own File and Edit menu options that apply specifically to the Data Grid window. There is also a Data Grid menu that enables you to add or remove rows and columns.

- A toolbar from which you can select the Model Type and Model Name you wish to apply to the dataset. When the dataset is ready for you to specify variables, press the Proceed button to display the Model Option screen.
- The Data Grid spreadsheet. From here, you can enter, edit, and sort data; rename columns; and perform mathematical transformations on columns.

PREDEFINED COLUMN TITLES FOR MODELS

New Data Grid windows are pre-loaded with column labels that work with the session templates provided with BMDS. The user can change the column labels, but should be aware that the dataset will not run in a BMDS session file unless the template option files in the session file are revised to recognize the new column label.

For the BMDS-provided session templates, the data grid contains pre-specified column labels as described in Table 27.

Table 20: *Column labels for template types*

Template Type	Pre-Specified Column Labels
Dichotomous	Dose, N, Effect
Nested	Dose, N, Response, Covariate
Continuous	Dose, N, Mean, Std

OPENING EXISTING DATASET FILES

When Open Dataset is chosen from the File menu or the Open Dataset button is pressed the user will be prompted for a file to load or import.

- Click the **Open Dataset** icon on the Toolbar, oror
- Select the **File>Open>Dataset (.dax)** option.

Selecting either option displays the Open dialog box. By default, BMDS initially displays any BMDS dataset files (*.dax) in the BMDS program directory's Data folder.

Note **Decimal Separators:** BMDS supports regional settings for the decimal separator in the user interface and in spreadsheets created by the Export to Excel function.

Thousands Separators: No “thousands separator” (regardless of regional setting) can be used in the data; that is, one thousand can only be written as 1000 rather than as 1,000.

See also:

Decimal and Thousands Separators in BMDS

CREATING A NEW DATASET

You can create a new dataset in any of the following ways:

- Click the **New Generic Dataset** button on the BMDS toolbar to open a new Data Grid window. A new Data Grid window contains 1000 rows and 50 columns.
- In a Session Grid window, right-click in the Data File column and select **New Data File (*.dax)** to open a new Data Grid window.
- Use the **File>New>Dataset (.dax)** menu and select one of the following options. Selecting an option opens a new Data Grid window with the selected Model Type and a default Model Name filled in, unless otherwise noted.
  - **Continuous Data**. Selecting this item displays another submenu, with the following options:
    - Summarized (Means & Stds)
    - Individual Response
  - Dichotomous Data
  - Nested Data.
  - **Generic Data.** For this option, Model Type and Model Name are blank.

See also:

Changing the Default Number of Rows and Columns

SELECTING A MODEL TO RUN

At the top of the Data Grid window are two fields where you specify the Model Type and then the specific Model you wish to apply to the dataset. Select the choices you want from the dropdown lists.

See also:

Model Types and Abbreviations

ENTERING OR IMPORTING DATA

If you opened an existing dataset file, then data will already be present in the Data Grid. However, if you selected the New Dataset option, then a blank Data grid window appears. From there, you can create a new dataset in a variety of ways.

Warning Do not import or create datasets that have two or more columns with the same name. BMDS calculations depend on the columns having unique names.

Note **Decimal Separators:** BMDS supports regional settings for the decimal separator in the user interface and in spreadsheets created by the Export to Excel function.

Thousands Separators: No "thousands separator" (regardless of regional setting) can be used in the data; that is, one thousand can only be written as 1000 rather than as 1,000.

Entering data

- You can manually type the data into individual cells of the Data Grid.
- You can copy and paste data using the standard Windows Cut-Copy-Paste commands from an Excel spreadsheet into the Data Grid.

Importing data

BMDS can import delimited DOS text files, files in Excel 2003 format, or BMDS 1.xx dataset files.

BMDS dataset files are stored as DOS text files delimited with blanks; each line represents a row in a spreadsheet and each blank signifies the start of a new value within the row. If your file has a similar format, then from the Data Grid's **File** menu you can choose either "BMDS 1.xx Dataset" if the file has a .set extension or "Space Delimited Text File."

You can import a dataset ***only*** into a blank Data Grid.

Note The first row of the imported file is reserved for column headers (variable names). Once imported, you can rename the column header. Column headers must be one word with no spaces.

5. From the BMDS toolbar, click the **New Generic Dataset** button. An empty Data Grid window is displayed.

6. From the Data Grid's **File** menu, select **Import Data From** and then the type of file you want to import. Valid file formats include:

- Tab-delimited text file (*.txt)
- Space-delimited text file (*.txt)
- Comma-separated values text file (*.csv)
- Excel 2003 (or earlier) spreadsheet (*.xls)
- BMDS 1.xx dataset (*.set)

See also:

- Renaming Columns
- Decimal and Thousands Separators in BMDS

COPYING, CUTTING, AND PASTING DATA

You can select one or multiple cells of data within BMDS and then use the standard Windows Cut (Ctrl+X), Copy (Ctrl+C), Paste (Ctrl+V), and Select All (Ctrl+A) commands to move the data wherever you like. These commands are also accessible from the BMDS application's **Edit** menu.

You can use these commands to transfer data to and from spreadsheet applications such as Excel and Lotus.

Selecting multiple sequential cells

Multiple cells can be copied or pasted at the same time.

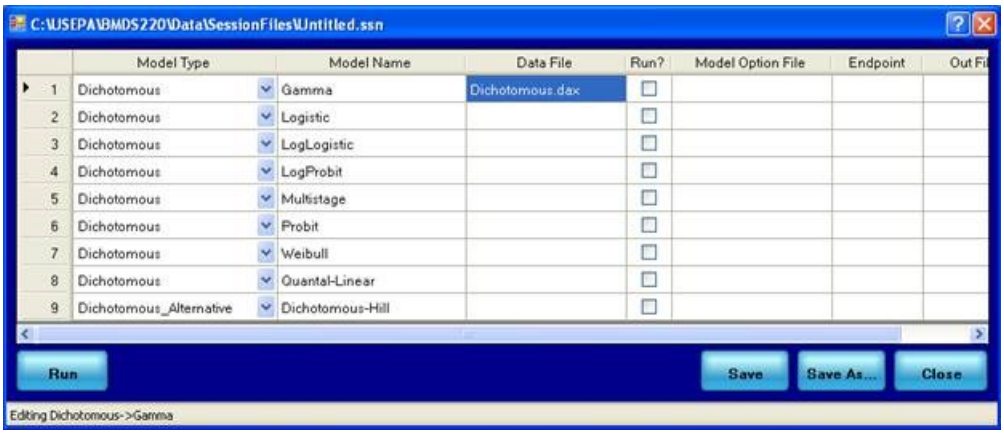
- Using the mouse: Click and drag to highlight the selected cells you want to copy or cut.
- Using the mouse and keyboard: Click on the first cell to select it. Press the Shift key and then click on the last cell to select all the cells.

Copying and pasting multiple cells of data

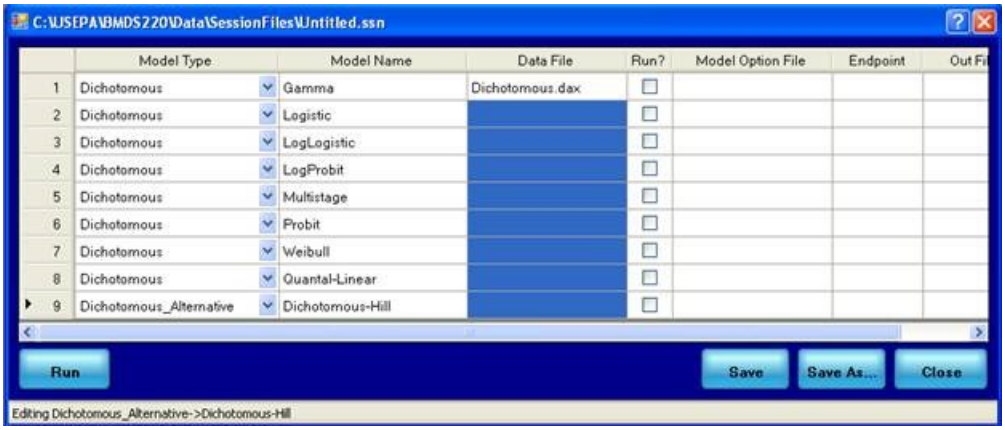
This technique enables you to copy or paste the same data file reference into multiple cells much more quickly than you could by doing so one at a time. This technique lets you to set the same data file for multiple models all at once. You could, for example, highlight five cells containing a data file reference, click on the first blank cell in a series, and then paste to insert the five references.

Note The amount of information you can paste is constrained by the number of empty cells. If only 3 cells are empty, and you have copied 10 cells, then only the three empty cells receive the pasted information.

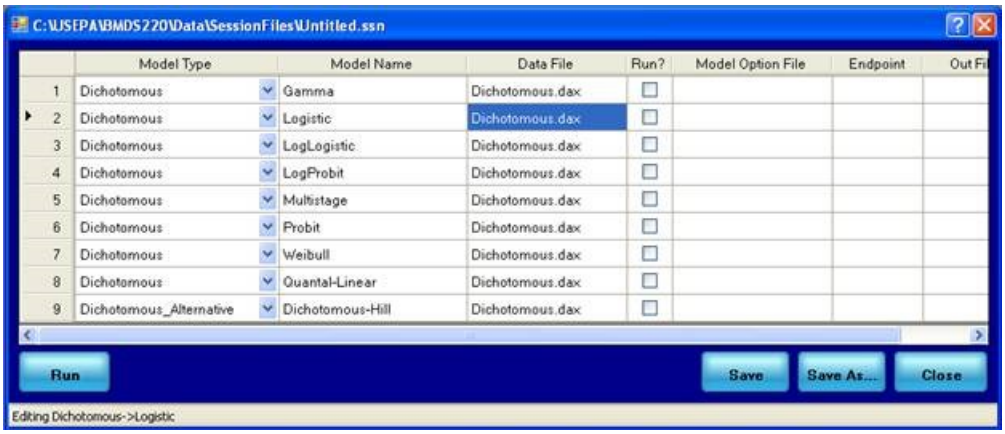
1. Select a cell that has the data file reference you want to copy, and press CTRL-C or select **Edit>Copy**.



2. Select the blank cells that will receive the copied data file value.



3. Press CTRL-V or select **Edit>Paste** to paste the data file value into the selected cells.



RENAMING COLUMNS

Data Grids are initially created with names in the form of Col1, Col2, Col3, and so on. You can rename columns in the Data Grid window to provide more meaningful names describing the data.

However, if you rename Data Grid's column labels, you must also revise the template option files in the BMDS session file so that BMDS can recognize the new column label. If you do not revise the template option files, then BMDS will not run the dataset with the revised column labels.

Column headers must be one word with no spaces.

1. Right-click on a column title to display a popup menu.
2. Select **Rename Column**. The Rename dialog box appears.

3. Enter a one-word title with no spaces. Valid column titles can include InterCapitaliZation, Punc.Tua.Tion, or Hy-Phens.
4. Select the **Save and Exit** button.

TRANSFORMING A COLUMN OF DATA

You can create a new data column in the Data Grid window by performing a mathematical operation on existing data fields.

1. In the Data Grid window, right-click on the column title.

2. Select **Transform Column** form the popup menu. The Variable Transformation dialog box appears.

3. Select an operation from the Transformation dropdown menu. Depending on the transformation, enter extra information as required. For example, for “SE to Standard Deviation,” specify the Data Grid column that holds the standard error value and the column that holds the value for Subjects in Dose Group. Or, for “Raise Column to Power X,” enter the column to be transformed and then the “X” value.
4. Click **OK**. The transformed data will appear in the designated column.

See also:

Data Transformation Types

DATA TRANSFORMATION TYPES

When you transform an existing data column in the Data Grid window, you direct BMDS to run a mathematical operation on the data to create a column of new data.

Not all transformations are valid for any possible data values. In general, ***you should be aware of what constitutes valid inputs for all of the transformations***. Be cautious when using the transformations if the goal is to derive valid numeric inputs for subsequent modeling.

You can direct BMDS to perform any of the following transformations.

Log Base 10 of a single column

This option will return the Log() base 10 of all values in the selected column.

Log Base e (Natural Log) of a single column

This option will return the Log() base e of all values in the selected column.

Note Be aware that not all transformations are valid for any possible data values. In particular, logarithmic transformations (log10 or natural log) of non-positive values will result in non-numeric values.

If you attempt a logarithmic transformation of 0 (which may occur when transforming the dose variable, when a control, or 0-valued, dose group is included), BMDS displays the result "-Infinity" for the transformed 0 value. This is consistent with the fact that the limit of log(x) is negative infinity as x approaches 0.

If you attempt a logarithmic transformation of a negative number, then BMDS displays the result "NaN," indicating that the result is "not a number."

Both "-Infinity" and "NaN" are not numeric values and should not be used as input for dose-response modeling; errors will occur if this is attempted.

Exponential Base 10 of a single column

This option will return 10 to the x where x is the value in the column for each row in that particular column.

Exponential Base e of a single column

This option will return e to the x where x is the value in the column for each row in that particular column.

Raise column to Power X

This option will raise each value in a column to a specified Power x, where x is a user specified number.

Multiply column by constant X

This option will multiply each value in a column by a specified constant x, where x is a user specified number.

Add two columns

This option will return the value of one column added to the value of a second column for each row in that particular column.

Subtract two columns

This option will return the value of one column minus the value of a second column for each row in that particular column.

Multiply two columns

This option will return the value of one column multiplied by the value of a second column for each row in that particular column.

Divide two columns

This option will return the value of one column divided by the value of a second column for each row in that particular column.

Quantilize column

This option will return either a 0 or a 1 for all rows based on whether the value in the selected column is Larger or Smaller than a user specified value. If the selected adverse direction is “Larger,” a 0 will be returned for values lower and a 1 will be returned for values larger than the user specified value. If the selected adverse direction is “Smaller,” a 1 will be returned for values lower and a 0 will be returned for values larger than the user specified value.

Add X to column

This option will add a constant X to each value in a column, where x is a user specified number.

SE to Standard Deviation (SD)

This option will convert standard errors (SE) from a designated column to standard deviations and place them in a designated SD column. The user must also designate the column that contains the number of subjects in each dose group as that value (n) is used in the calculation.

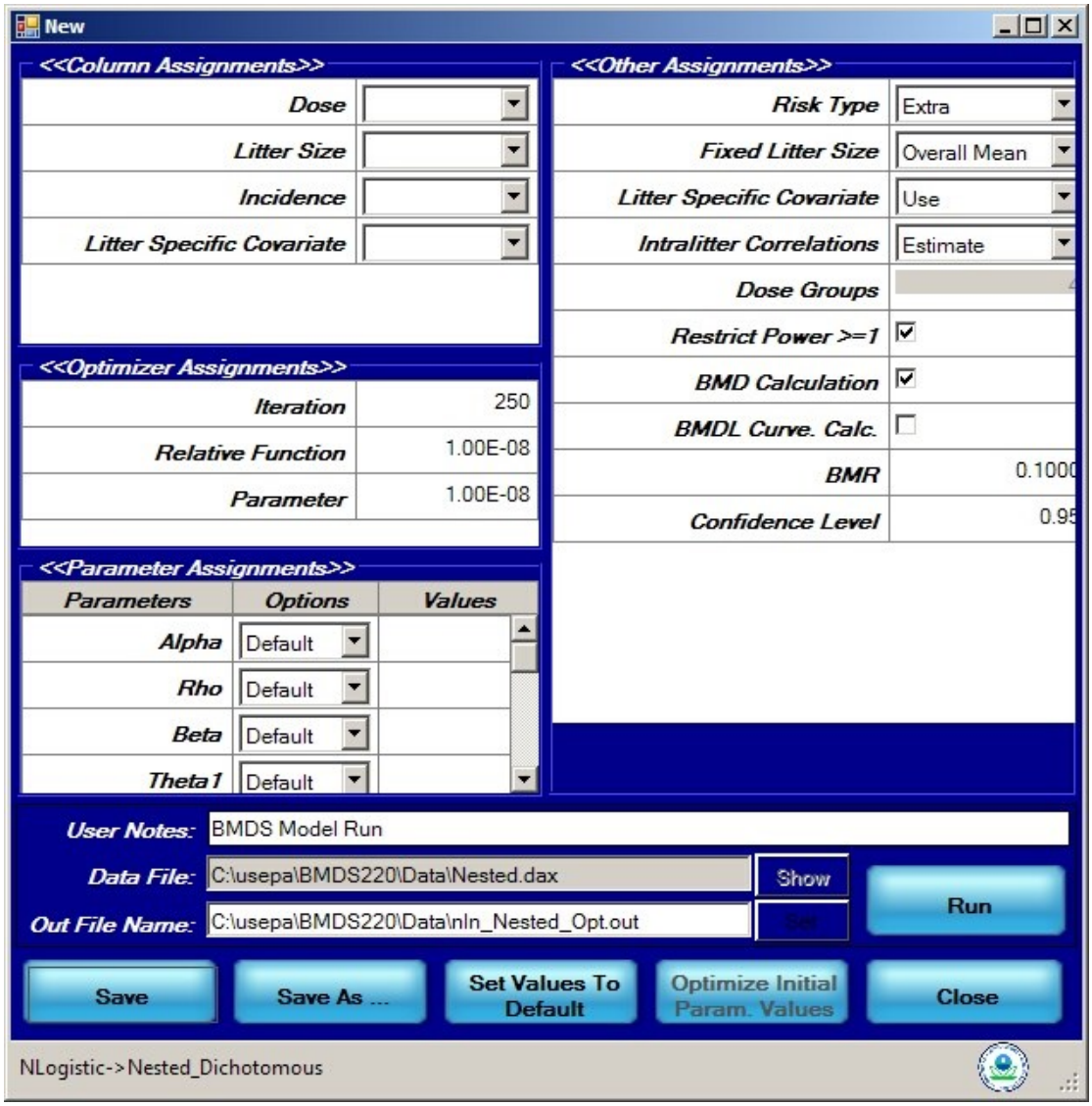
See also:

Transforming a Column of Data

DEFINING MODEL OPTIONS AND DATASET VARIABLES

After you click the Data Grid window's **Proceed** button, BMDS displays the Model Option Screen.

BMDS will display the Model Option Screen appropriate to the model chosen on the Data Grid window. The following screenshot shows the Model Option Screen for the NLogistic Nested Dichotomous model.



From this option screen, the user assigns columns in the dataset to the required variables and selects the model options (e.g., parameter constraints and BMRF values). When these choices are complete, click the **Run** button to complete the analysis of the selected dataset.

All of the variables required for a model must be linked to a column in the spreadsheet. Variables required for running BMDS on a dataset will differ according to the Model Type selected; these variables appear in the “Column Assignments” section of the Model Option Screen for the chosen model.

Table 21 describes the required variables for each model type.

Table 21: *Required variables for BMDS model types*

Model Types	Required Variables
Dichotomous and Dichotomous_Alternative	• Dose • # Subjects in Dose Group • Incidence or % Positive
Continuous	If response data are reported by dose group, then the following columns in the Data Grid must be identified: • Dose • # Subjects in Dose Group • Mean • Standard Deviation If response data are reported for each individual animal, then the following columns must be identified: • Dose • Response
Nested	• Dose • Litter Specific Covariate • Incidence • Litter Size

The Model Option Screens and analysis requirements for a Rptd_Resp_Measures, or Conc x Time model are somewhat different and are discussed elsewhere in this documentation.

The following sections describe the variables mentioned above in more detail.

Dose

Variable representing the amount of a substance an experimental subject consumes (e.g., oral drinking water or food studies), is injected with (e.g., gavage or intravenous injection studies), or is exposed to (e.g., inhalation studies). For inhalation studies, this column would represent the concentration of the substance in the air being inhaled. Most of the time Dose will be an independent variable under the control of the experimenter. However, for epidemiological studies Dose, as well as confounding factors such as age, smoking habits and duration of exposure, are not under the control of the experimenter and may be different for each individual responder. While BMDS allows for the entry and analysis of individual Dose information, provisions for factoring the impact of confounders have not as yet been incorporated.

#Subjects in Dose Group

Independent variable representing the total number of subjects within a dose group for which a continuous Response is measured or dichotomous Incidence is identified.

Incidence

Dependent variable used for Dichotomous and Nested Models to represent the number of subjects within a Dose group responding in a positive, generally considered adverse, manner.

% Positive

Dependent variable used for Dichotomous Models to represent the percent of the total number of subjects within a Dose group that responded positively. The data for this column must be entered as a percent, not a fraction.

Mean

Dependent variable used for Continuous Models to represent the average response within a group (sum of all responses in group divided by Subjects/Group).

Standard Deviation

The positive square root of the variance for a Dose group, which is the sum of the squared deviations of the individual responses from the mean, divided by # Subjects in Dose Group-1.

Response

This dependent variable refers to the individual continuous data responses by subject. If this variable is used, the Subjects/Group, Mean and Standard Deviation continuous data variables are not used and are grayed out.

Litter Size

Number of live pups per litter.

Litter Specific Covariate

This is a covariate such as body weight of dams, number of implants or litter size that is felt to best explain response variability between litters. It is used in the nested models to try to account for that variability. See Nested Model Descriptions for more details.

See also:

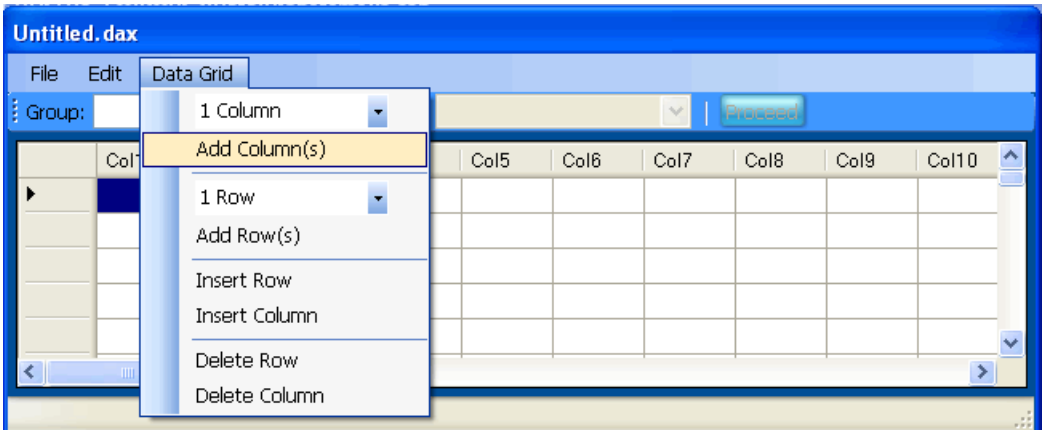
Appendix B: Model Options Screen Fields Reference

ADDING AND DELETING DATA GRID COLUMNS AND ROWS

You can add columns and rows to, and delete rows from, Session Grids and Data Grids.

You can delete columns from Data Grids only.

Note When all of the cells in a column/row are empty the column/row is removed when the dataset is saved. However, if a column/row contains any data at all, the column/row is retained when the dataset is saved.



- To insert a row above the currently selected row, select **Data Grid>Insert Row**.
- To delete the currently selected row, select **Data Grid>Delete Row**.
- To add multiple rows above the currently selected row, select **Data Grid**, pick a predefined number of rows to add from the picklist (1, 2, 5, 10, 50, or 100), and click **Add Row(s)**.
- To insert a column to the left of the currently selected column, select **Data Grid>Insert Column**. In the Set Name dialog box, enter a name for the new column and click **Save and Exit**.
- To delete the currently selected column, select **Data Grid>Delete Column**.
- To insert multiple columns, select **Data Grid**, pick a predefined number of columns from the picklist (1, 2, 5, or 10), click **Add Column(s)**, enter titles for the new columns in the Set Name dialog box, and click **Save and Exit**. The new columns are added to the rightmost side of the Data Grid window.

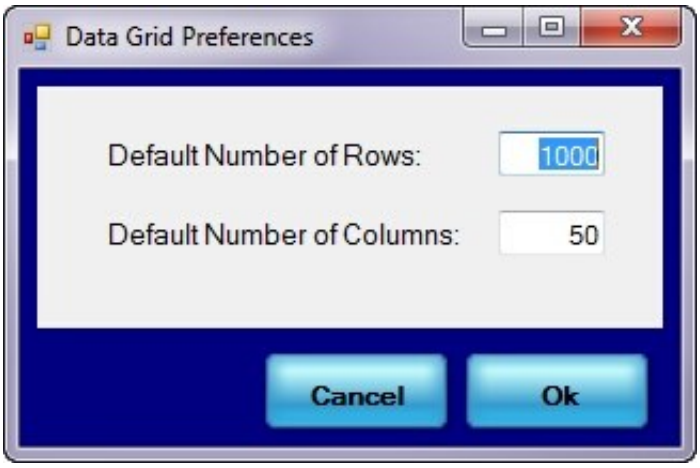
See also:

- Working with the Menus, Tool Bars, & Status Bars
- Adding and Deleting Session Grid Rows

CHANGING THE DEFAULT NUMBER OF ROWS AND COLUMNS

The BMDS Data Grid windows default to 1000 rows and 50 columns. These defaults are easily changed.

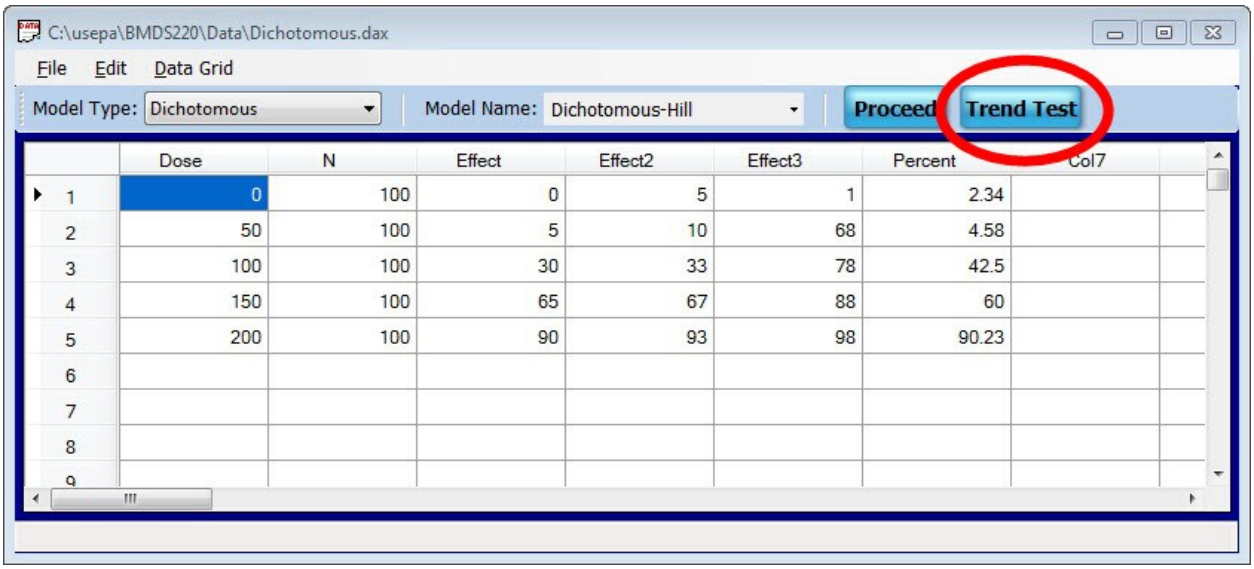
1. From the BMDS application window, select **Tools>Preferences**, and select Data Grid to display its Preferences dialog box.



2. Enter new values in the appropriate fields.
3. Click **OK**.

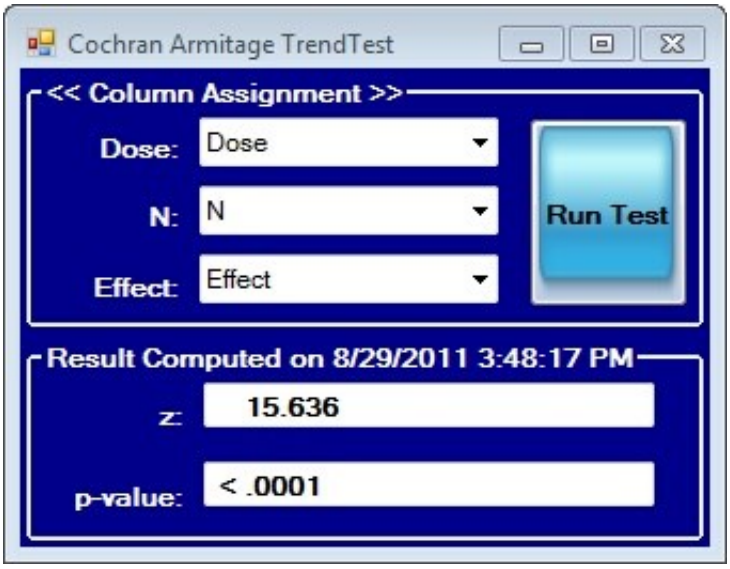
RUNNING TREND TESTS

When the user opens a dataset (or creates a new dataset and fills in the body of that new file), and if that dataset is identified as appropriate for a Dichotomous or Dichotomous_Alternative Model Type (the Model Type is selected to be Dichotomous or Dichotomous_Alternative), the **Trend Test** button (upper right corner of the Data Grid window) becomes active.



Clicking the **Trend Test** button implements a Cochran-Armitage trend test (cf. Haseman, 1984, "Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies", *Environmental Health Perspectives*, 58, p. 385). That test is used to determine if there appears to be a dose-related trend in response.

If the user has selected a dataset with the default column headers (Dose, N, Effect), then the Trend Test screen that appears (as shown below) will show the calculated test statistic value (z) and the associated p-value. This can be verified by observing that the time-date stamp on the trend test screen is the current time and date. The user can select other column headers for the dose, sample size (N), and/or effect variable and run the test again by clicking the **Run Test** button.



If the columns headers in the dataset are not Dose, N, and Effect (i.e., if BMDS cannot find any one of those column headers in the dataset), then the trend test

will ***NOT*** be automatically implemented; the user ***MUST*** enter the appropriate column headers in the trend test screen and click the **Run Test** button.

For interpretation, a p-value that is small (e.g., less than 0.05) indicates the presence of a dose-related trend.

SORTING DATA

In the Data Grid window, left-click on a column header to sort the dataset by that column's values. Click again to toggle between ascending order and descending order for the sort.

An up-pointing triangle in a column indicates that its values are sorted ascending; a down-pointing triangle indicates a descending sort order.

You must save the dataset to retain the sort order.

Note	Sorts only work with numeric data and non-empty cells. Enter a zero in an empty cell to ensure proper sorting.

EXPORTING DATA

Using BMDS, you can export a dataset to delimited text files that can be imported into other applications for further analysis.

1. With a dataset loaded, from the Data Grid menubar select **File>Export Data To** and select one of the following options:

- Tab-delimited text file (*.txt)
- Space-delimited text file (*.txt)
- Comma-separated values text file (*.csv)

2. In the Save As dialog box, specify a file name and location for the export file and select **Save**.

SAVING A DATASET

The dataset's file name is shown in the Data Grid's title bar, as shown below. If you opened the dataset from within a Session Grid window, then the filename in the Data Grid's title bar should match the filename in the Session Grid's Data File column.

Newly created data sets are initially assigned a default name of “Untitled.”

If a model is run on a dataset before it is saved to another name, the results of the model run are saved to the root directory of the BMDS program.

It is recommended that you save datasets to a unique directory. The Data subdirectory within the BMDS program directory is usually a good location for consolidating your BMDS data files.

Saving changes to the current dataset

From the Data Grid's File menu, select Save Dataset. BMDS will save any changes to the dataset file name that is displayed in the Data Grid's title bar.

Saving a dataset to a different name and directory location

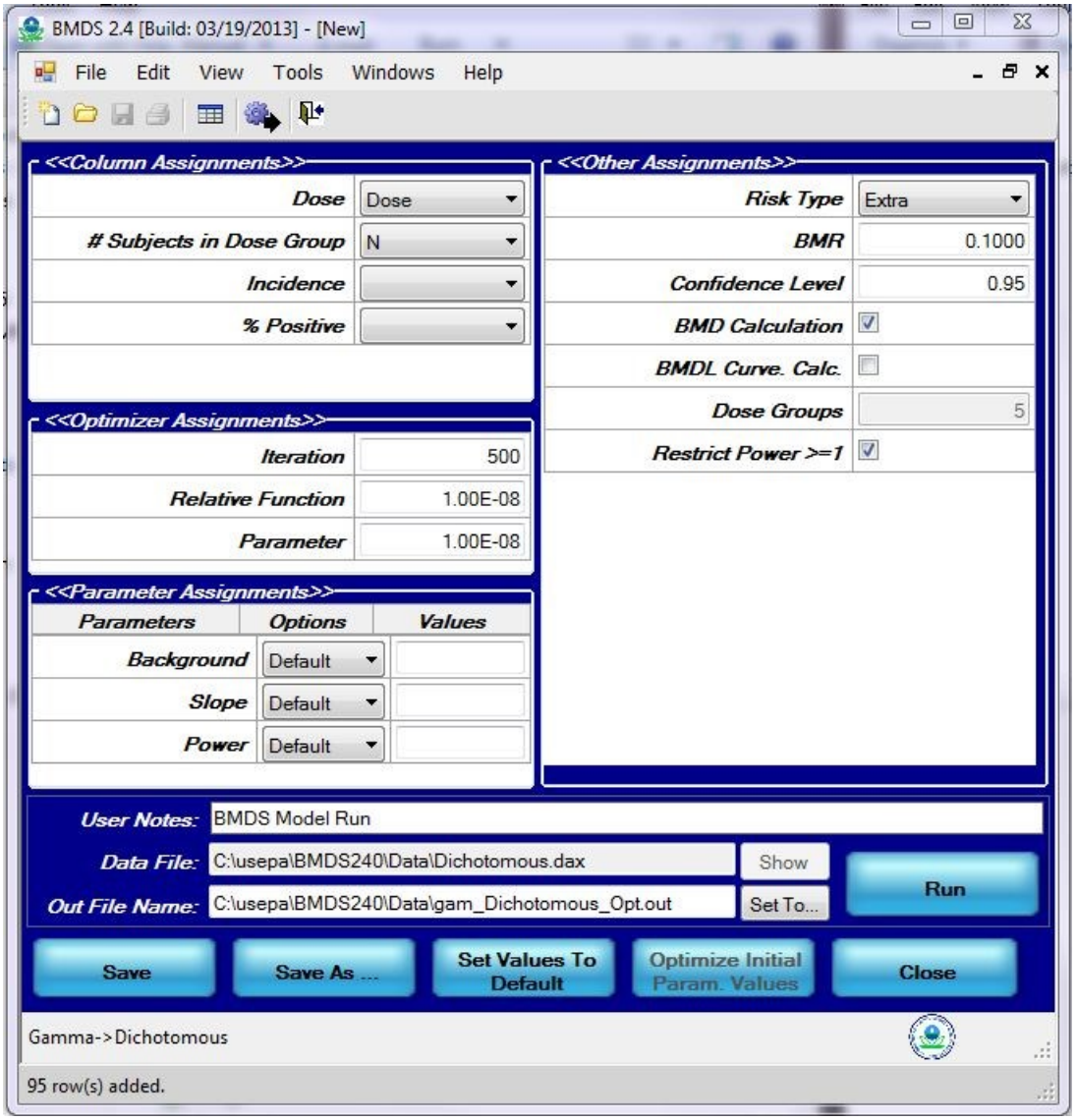
1. From the Data Grid's File menu, select “Save Dataset As . . .”
2. The Save As dialog box displays. Enter a new file name in the File Name field.
3. The Save As dialog box defaults to the Data subdirectory of the BMDS program directory. If you want to save the file to a different location, navigate to that location and click Save.
4. BMDS saves the new file as a BMDS dataset with a .dax extension.

Note For result files (such as .out and .plt) from model runs on a single dataset (***not*** when run from a session), BMDS prefixes the dataset's file name and saves the files to the same directory as the .dax file.

WORKING WITH THE MODEL OPTION SCREEN

When you click the **Proceed** button on the Data Grid window, the Model Option screen is displayed. The Model Option screen lets users change options available for a model run.

When BMDS is initially run or when the **Set Values to Defaults** button is selected, all options are set to their default values. Options chosen and saved to an Option file with the ".opt" extension are retained for later use.



Each Model Option screen contains features that are unique to the model being run. However, all Model Option screens share the following common features:

Model Type and Name

The status bar In the lower left corner of the Model Option screen displays the name of the specific model being employed and the model type (Dichotomous, Continuous, Nested, Dichotomous Alternative, or Repeated Response Measures).

User Notes field

This is an editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.

Data File field

A field displaying the name of the data file (*.dax) file.

Out File Name field

Displays the output path and file name. Click the **Set** button to change the file name and/or location.

Column Assignments section

This section allows the user to assign columns from the data file to the parameters that are required for model runs.

Optimizer Assignments section

This section specifies information controlling the determination of convergence of the model runs. In general, you can safely leave these settings at their default values.

- Iteration: An upper limit to the number of iterations that will be used in the optimizations (default = 250).
- Relative Function: This specifies the criterion for ascertaining relative function convergence (default = 1.0e-8)
- Parameter Function: This specifies the criterion for ascertaining parameter convergence (default = 1.0e-8)

Parameter Assignments section

The user can choose one of three options related to parameter values:

- Default option: the initial estimated value for a parameter is determined by the program and its value will vary during optimizations.
- Specified option: the initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations.
- Initialized option: the initial estimated value for a parameter is entered by the user but its value will vary during optimizations. ***If the Initialized***

option is checked for any parameter, the user must choose the Specified or Initialized option for all parameters.

Other Assignments section

This section contains information on parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

- BMD Calculation: Specifies whether or not the user wants a BMD (with associated BMDL) calculated.
- BMDL Curve Calc: When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).
- Confidence Level: The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.
- BMRF: The factor defining the benchmark response level. Its value will depend on the Risk Type or BMR Type specified by the user (one of these types will also be in the Other Assignments section, depending on the model type).

Other Buttons

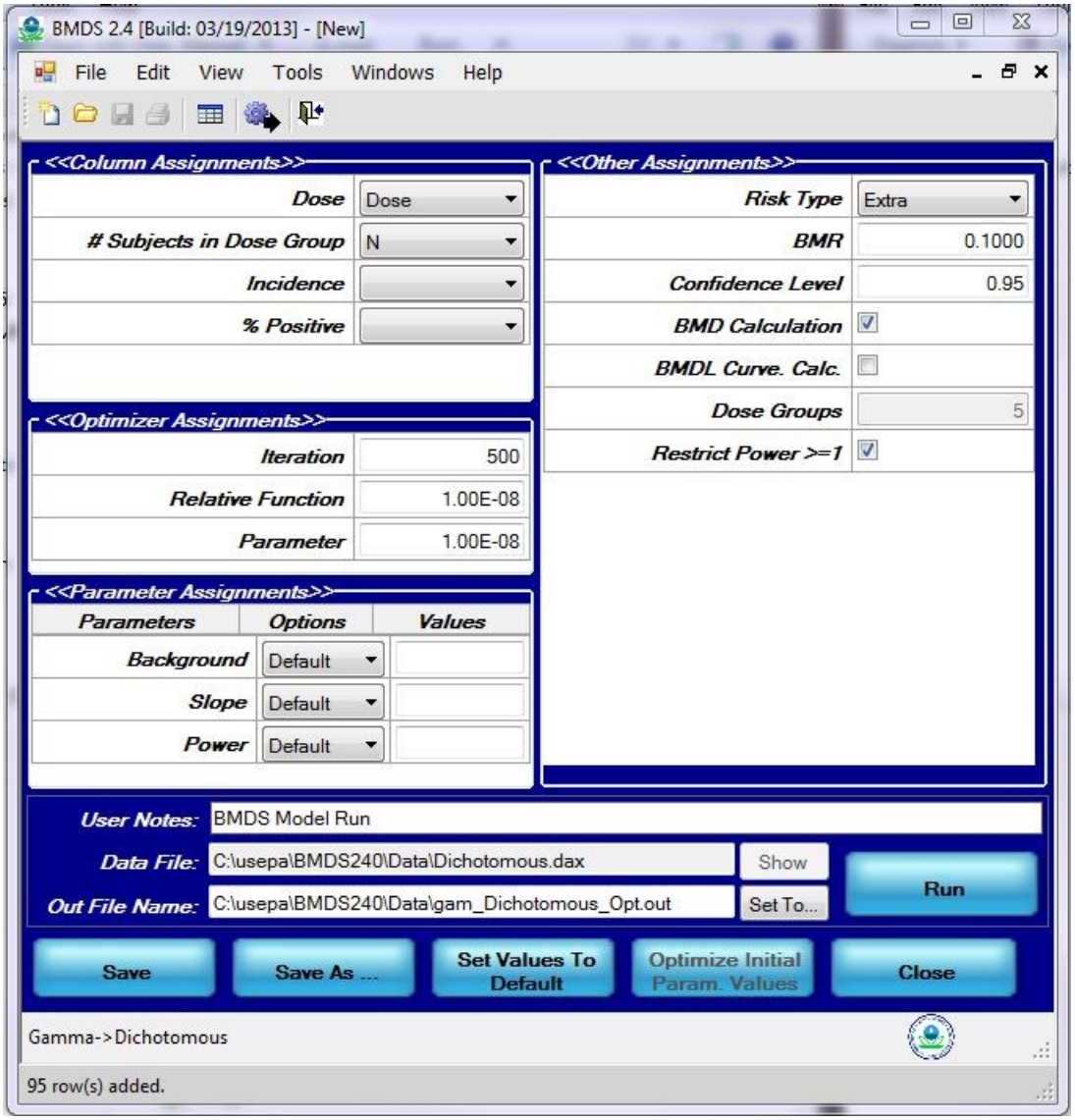
- **Save**. Save the current Model Option settings to an .opt file.
- **Save As …**Save the current options under a different file name.
- **Set Values to Defaults.** Return values to their defaults for the selected model.
- Optimize Initial Param. Values.
- **Run**. Run the model using the current option settings.
- **Close**. Close the Model Option screen.

See also:

Using Session and Option File Templates

DICHOTOMOUS AND DICHOTOMOUS_ALTERNATIVE MODEL OPTION SCREENS

All of the common options described in Working with the Model Option Screen are available on the Model Option screen for Dichotomous and Dichotomous_Alternative models. In addition, the options described in this section are available in all Option screens for dichotomous models.



Dose Groups

This is a read-only field indicating the number of Dose groups recorded from the dataset file for input into the model.

Risk Type

Choices are “Extra” (Default) or “Added.” Added risk is the additional proportion of total animals that respond in the presence of the dose, or the predicted probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1—P(0). *The BMRF for all dichotomous models must be between 0 and 1 (not inclusive).*

Note about BMRF and Graphs

The response associated with the BMR that is displayed in the graphical model output will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response value one must solve for P(d) in the equation for added or extra risk discussed above. *In addition to the two options listed above for all dichotomous models, the following options are available for specific models of the Dichotomous or Dichotomous_Alternative Type.*

Restrict Slope >= 1

Models: LogLogistic, Log-Probit, Dichotomous-Hill

Selecting this feature (Default for LogLogistic and Dichotomous Hill models) restricts the slope parameter (β) to a value of 1 or greater. For the LogLogistic and Dichotomous Hill models, if β < 1, the slope of the dose-response curve becomes infinite at the control dose. For the LogProbit and LogProbit-BgDose models, the slope of the dose-response curve can be very steep at low doses at or below the BMD or BMDL, before it becomes smaller approaching zero dose. Such characteristics, for all four models, may be biologically unrealistic, and can lead to numerical problems.

Restrict Power >= 1

Models: Gamma , Weibull

Selecting this feature (Default) restricts the power parameter (α) to a value of 1 or greater. If **α < 1**, then the slope of the dose-response curve becomes infinite at the control dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so EPA recommends restricting **α >= 1**

Degree of Polynomial

Models: Multistage, Multistage-Cancer

This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 23). A value must be entered here before the model will run. Polynomial degree should not

exceed the number of dose groups unless the beta coefficients of the model are specified or restricted (beta coefficients are always restricted in the multistage-cancer model).

Restrict Betas >= 0

Models: Multistage

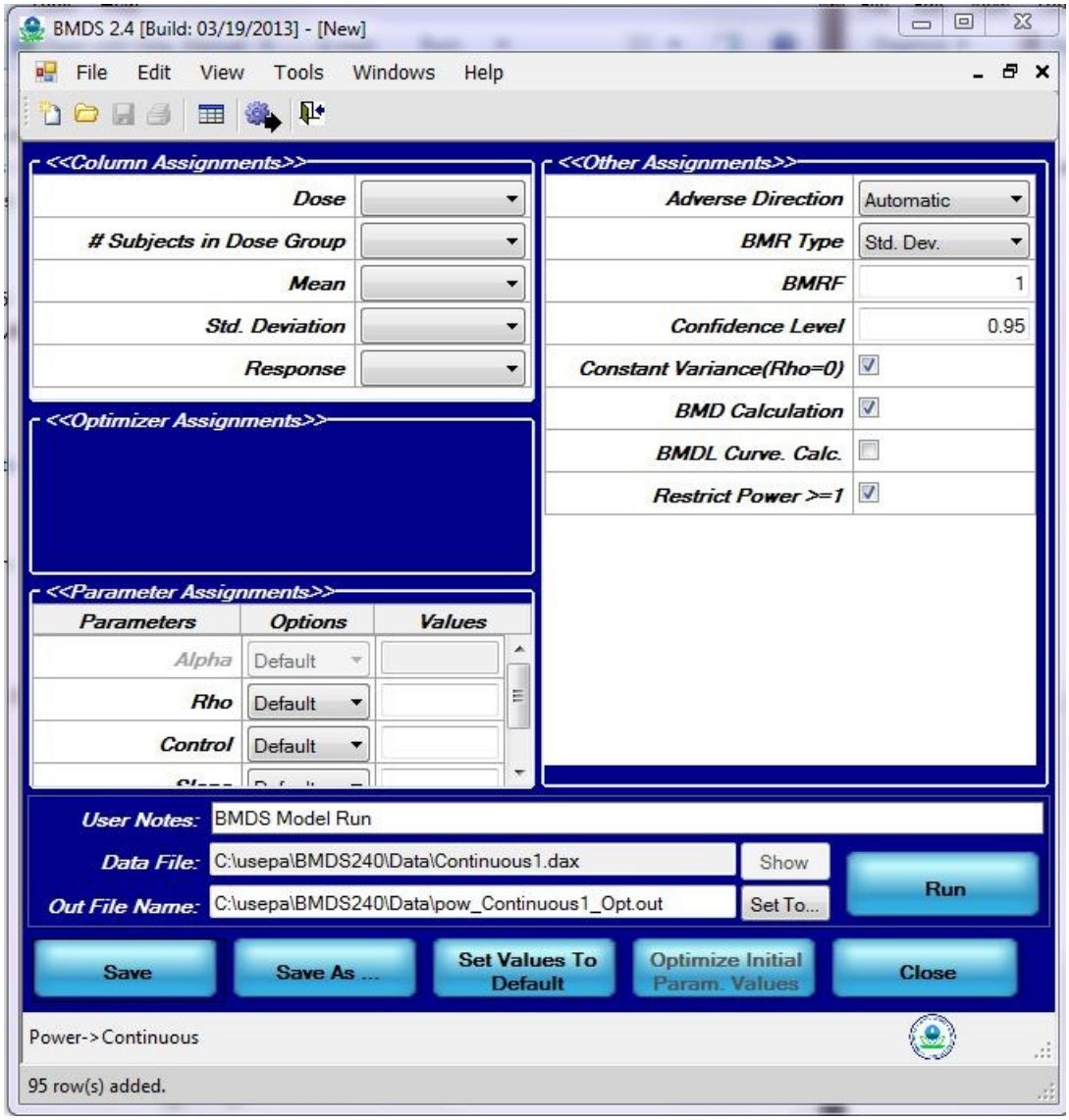
Selecting this feature (Default) restricts all of the beta (β) parameter coefficients in the multistage model to a value of 0 or greater.

See also:

- Dichotomous Model Options Fields
- Dichotomous_Alternative Model Options Fields
- Dichotomous Model Descriptions
- Dichotomous Models—Text Output

CONTINUOUS MODEL OPTION SCREENS

All of the common options described in Working with the Model Option Screen are available on the Model Option screen for Continuous models. In addition, the options discussed in this section are available in all Model Option screens for Continuous models.



Constant Variance

When selected (Default), the model assumes a constant variance across all dose groups. If not selected, then the model assumes that the variance can be different for each dose group, and varies as a power function of the mean response (see Continuous Model Descriptions for more details).

Adverse Direction

Choices for the Adverse Direction option are “Automatic,” (Default), “Up” or “Down.” This option refers to whether adversity increases as the dose-response curve rises “up” or falls “down.” If automatic is chosen, the software chooses the adverse direction based on the shape of the dose-response curve. Manually choose the adverse direction if you know the direction of adversity for the endpoint being studied. This selection only impacts how the

user-designated BMR is used in conjunction with model results to obtain the BMD.

BMR Type

The BMR type is the method of choice for defining the response level used to derive the benchmark dose (BMD). The choices allowed are “Rel. Dev.” (Default), “Abs. Dev.,” “Std. Dev.,” “Point” and “Extra” (Hill model only).

Rel. Dev. (Relative Deviation) means the response associated with the BMR will be the background estimate plus or minus (depending on the Adverse Direction) the product of the background estimate times the BMRF entered by the user.

Abs. Dev. (Absolute Deviation) means the response associated with the BMR will be the background estimate plus or minus the BMRF.

Std. Dev. (Standard Deviation) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the standard deviation for the control group data.

Point means the response associated with the BMR will be the BMRF value itself.

Extra (Hill only) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the difference between the background estimate and the model estimate of the maximum/minimum response. “Extra” is similar to Extra risk for dichotomous data, except that the maximum (or minimum) achievable response is not 1, but is estimated from the model.

Rel. Dev.Response = m(0) + (BMRF* m(0)) (Default)

Abs. Dev.Response = m(0) + BMRF

Std. Dev.Response = m(0) + (BMRF*STD)

Point Response = BMRF

Extra (Hill and some exponential models only)

for “up” Response = m(0) + (BMRF*(mmax—m(0)))

for “down” Response = m(0)—(BMRF*(m(0)—mmin))

where m(0) is the mean response when exposure equals zero, STD is the standard deviation when exposure equals zero, mmax is the maximum predicted mean from the Hill or exponential model, and mmin is the minimum predicted mean from the Hill or exponential model.

Note When response data is lognormally distributed, the BMR Types acquire different meanings. As of BMDS 2.6.0.1, only continuous exponential models can assume lognormal distribution. For more information, refer to Unique Options for Exponential Models.

In addition to the three options listed above for all continuous models, the following options are available for specific continuous models.

Degree Poly

Models: Linear, Polynomial

This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 21). A value must be entered here before the model will run. Polynomial degree should not exceed the number of dose groups unless the beta coefficients of the model are restricted. For the linear model, this field is set to 1 and is not editable.

Restrict Power >= 1

Models: Power, Exponential

The power parameter can be restricted to be greater than or equal to one. The power is unrestricted if this option is not selected. This option is currently disabled for the exponential models.

Restrict n > 1

Model: Hill

The n parameter of the Hill model can be restricted to be greater than one. The n parameter is unrestricted if this option is not selected.

Restriction

Linear, Polynomial

Restrictions on coefficients of the dose terms can be “None” (Default), “Non-negative” (>0), or “Non-positive” (<0). Note that, while no restrictions (None) is the current default for this option, the user should specify that the parameters be restricted to either Non-negative or Non-positive values whenever possible to avoid “wavy” model responses (see details in Polynomial Model description). Since there is only one dose coefficient in the continuous Linear model, this is sometimes referred to as restricting the slope of this model.

BMDL Curve Calculation

Linear, Polynomial, Power

When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, ***the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary*** (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).

See also:

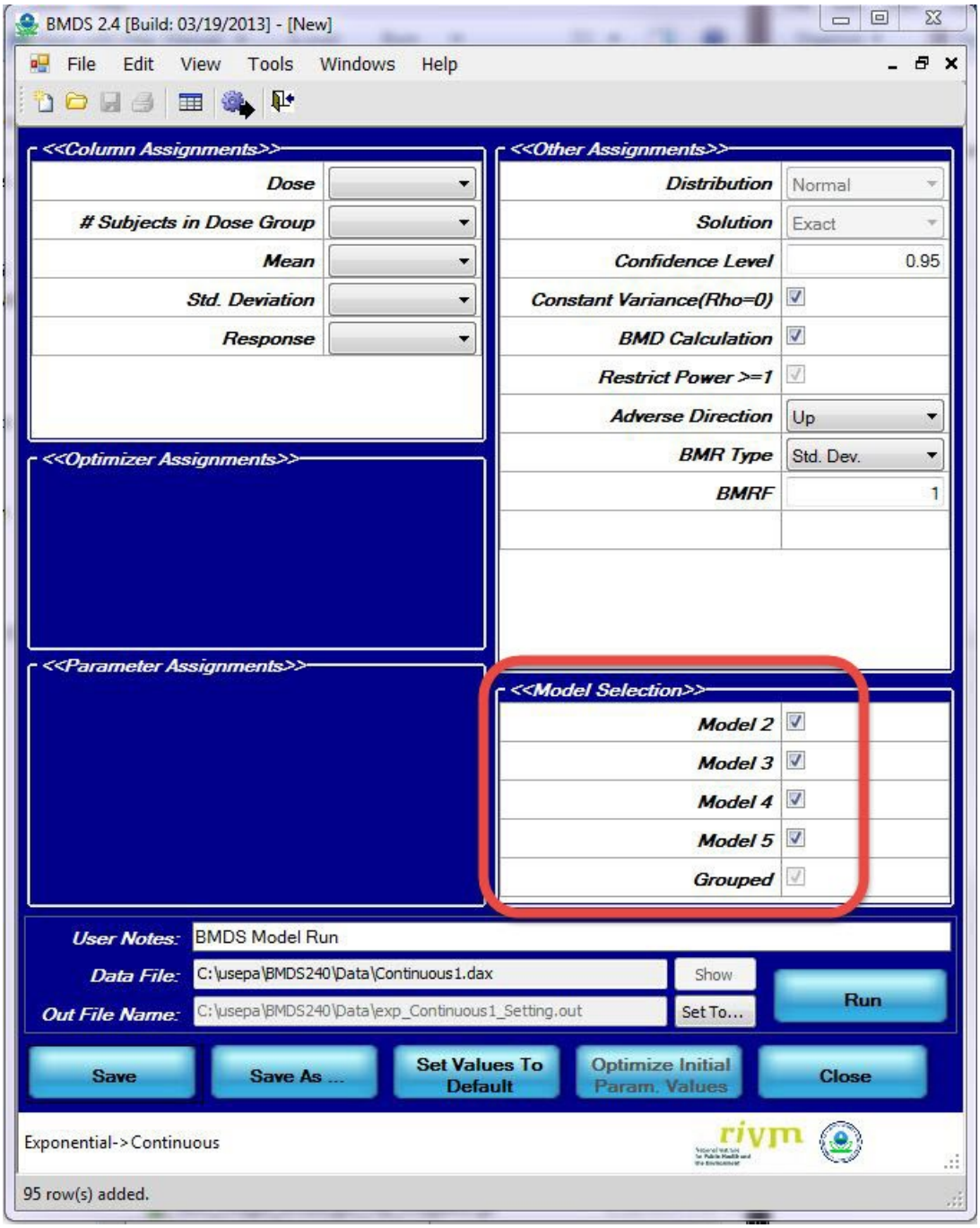
- Continuous Model Options Fields
- Continuous Models—Descriptions
- Continuous Models—Text Output
- Unique Options for Exponential Models

Unique Options for Exponential Models

The exponential model choice actually allows the user to run up to four models that have exponential-dose terms. These models are referred to as exponential Models 2–5 (following a designation by Dr. Wout Slob, wherein the restricted (flat) model was model 1). Refer to the section on Exponential Continuous Model Description for additional details.

The user may choose to run any or all of the exponential models when running from a Session screen. (When running on a single dataset by use of the data grid, all exponential models will be run.)

Moreover, the user may select to have the exponential model runs reported (grouped) together in one output file or on separate output files. These choices are made in the Model Selection section of the exponential model option screen:



Other options unique to the exponential model option screen are as follows:

Distribution: The user may choose to assume that the data are normally or lognormally distributed around the dose-group-specific means. The choice of the distribution affects that type of MLE solution that may be obtained (see next option). Moreover, when a lognormal distribution is assumed, only constant (log-scale) variance models will be fit to the data; such models correspond to an assumption of a constant coefficient of variation.

Solution: The user may choose to get an exact or approximate MLE solution. When the data are assumed to be normally distributed, the choice is fixed at "Exact" because the exact solution is available no matter how the data are presented (either as group-specific means and variances or as individual responses). When the data are assumed to be lognormally distributed and the data are presented in terms of group-specific means and standard deviations, then the exact MLE solution can not be obtained. In that case, the "Solution" option is fixed at "Approximate" and the means and standard deviations of the log-transformed data are estimated as follows:

log-scale mean = ln(mean)—ln(1+(std/mean)2)/2

log-scale std = sqrt[ln(1+(std/mean)2)]

When the data are assumed to be lognormally distributed and the individual responses are available the user may choose between the exact and approximate solutions. In this case, the user is advised to select the exact solution; the only reason to select the approximate solution in this case would be to compare it to other calculations that were done approximately out of necessity.

Also note that in the "Parameter Assignments" section, each model has a separate tab to allow model-specific parameter designations (the default, specified, and initialized options discussed above).

Definition of BMR Types under Lognormal Distribution Assumption

The Exponential models allow the user to assume that the response data are lognormally distributed, with median values defined by the dose-response function and a constant log-scale variance. Under such an assumption the BMR types are defined and implemented so that they are calculated by the program to return BMDs as follows (where BMRF is the numerical value, specified by the user, indicating the response, or change in response, of interest):

Relative Deviation: The natural scale median value at the BMD, m(BMD), differs from the natural scale median at 0 dose, m(0), such that |m(BMD)—m(0)|/m(0) = BMRF.

Absolute Deviation: The natural scale median value at the BMD, m(BMD), differs from the natural scale median at 0 dose, m(0), such that |m(BMD)—m(0)| = BMRF.

Standard deviation: The log-scale mean at the BMD, ln(m(BMD)), differs from the log-scale mean at 0 dose, ln(m(0)), such that |ln(m(BMD))—ln(m(0))|/σ(0) = BMRF, where σ(0) is the log-scale standard deviation at 0 dose. Recall that σ(0) = ln(GSD(0)). This definition allows the user to use BMRF's typical of an analysis where a normal distribution of responses is

assumed (e.g., the EPA default of 1 standard deviation) and still maintain the logic and rationale for such choices, since the log-transformed response values under the lognormal assumption would themselves be normally distributed.

Point: The natural scale median value at the BMD, m(BMD), equals the BMRF, i.e., m(BMD) = BMRF.

See also:

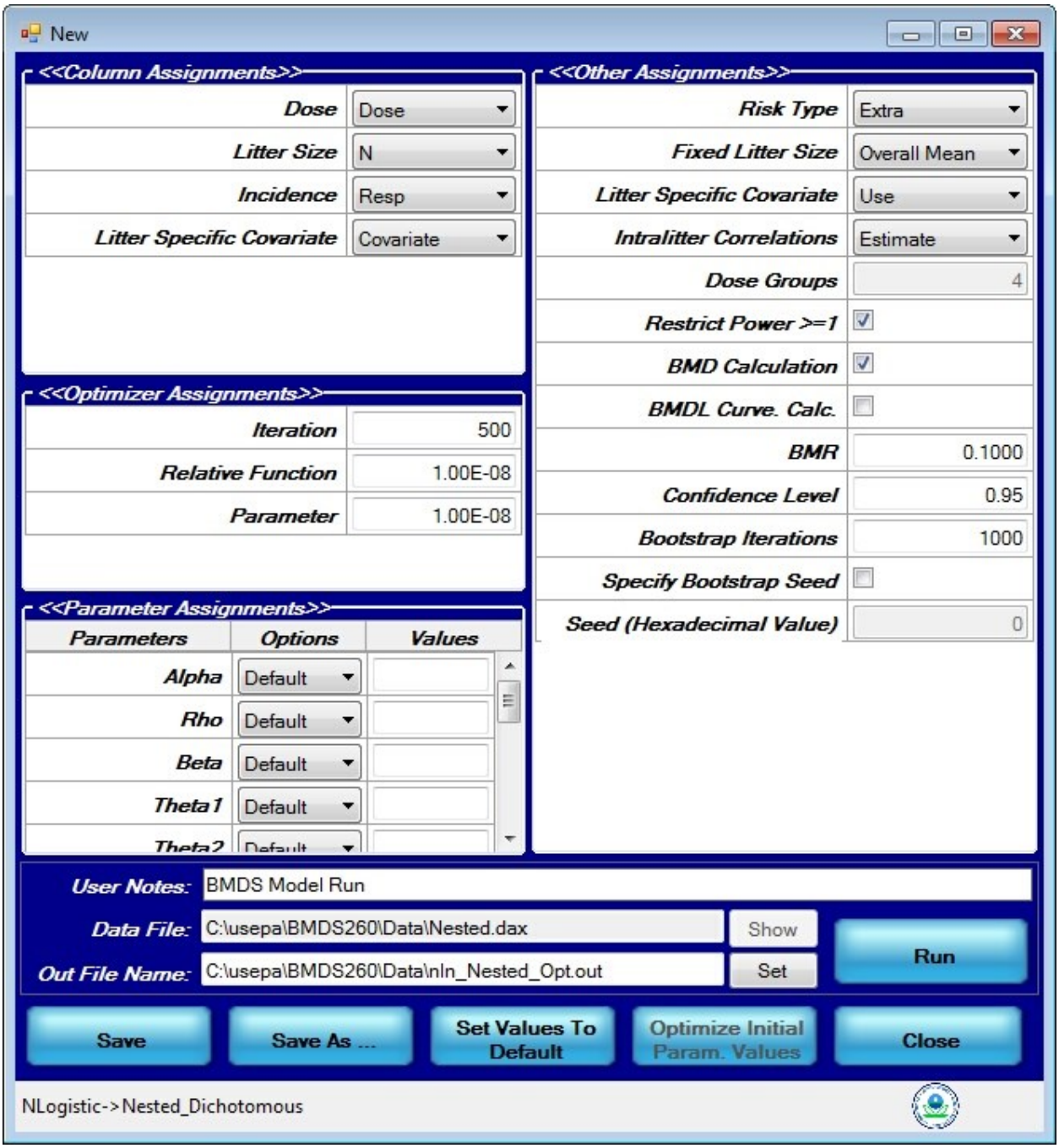
- Continuous Exponential Model Options Fields
- Continuous Models—Descriptions
- Continuous Models—Text Output
- Exponential Continuous Models—Description

NESTED MODEL OPTION SCREEN

All of the common options described in Working with the Model Option Screen are available on the Model Option screen for Nested models. In addition, the options discussed in this section are available in all Model Option screens for Nested models.

Note that in the “Column Assignments” section, the parameter “Litter Size” replaced “#Subjects in Group” from earlier BMDS versions. Also, an additional parameter, “Litter Specific Covariate,” has been added. These designations reflect the primary use of the nested models, i.e., for modeling data from reproductive or developmental assays in which the number of responders within litters of certain sizes are recorded.

The options described in the rest of this section are available in all Option screens for nested models.



Risk Type

Choices are “Extra” or “Added.” Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1—P(0). Thus, extra and additional risk are equal when background rate is zero.

Fixed Litter Size

Choices are “Control Group Mean” (Default) or “Overall Mean.” See Nested Model Descriptions for an explanation as to why this option is necessary, and which choice would be preferred for your given dataset. Basically, if the Litter Specific Covariate is not affected by dose, the Overall Mean should be used. If the Litter Specific Covariate is affected by dose, consider using the Control Group Mean.

Litter Specific Covariate

Provides user with the option to allow the models to attempt to account for a litter specific covariate or not. If “Use Litter Specific Covariate” is selected (Default), all of the Theta values are estimated . If “Don't Use Litter Specific Covariate” is chosen, all of the Theta values are set to zero.

Intralitter Correlations

Provides user with the option to allow the models to attempt to estimate intralitter correlations or assume they are zero. If “Estimate Intralitter Correlations” is selected (Default), all of the Phi values are estimated (one for each dose group). If “Assume Intralitter Correlations Zero” is chosen, all of the Phi values are set to zero.

Dose Groups

This is a read-only field indicating the number of Dose groups recorded from the dataset file for input into the model.

Restrict Power >=1

Power parameter can be restricted to be > 1 (Default)

Bootstrap Iterations

Specify the number of bootstrap iterations (default is 1000) to run to estimate goodness of fit. It is recommended to keep the value at a minimum of 1000.

Specify Bootstrap Seed

Select this feature to specify a bootstrap seed for the random number generator. Default is that BMDS auto-generates a seed for the random number generator based on the system clock.

Seed (Hexadecimal Value)

If **Specify Bootstrap Seed** is selected, enter the value here in hexadecimal form. Example: “1E240”.

See also:

- Nested Model Options Fields

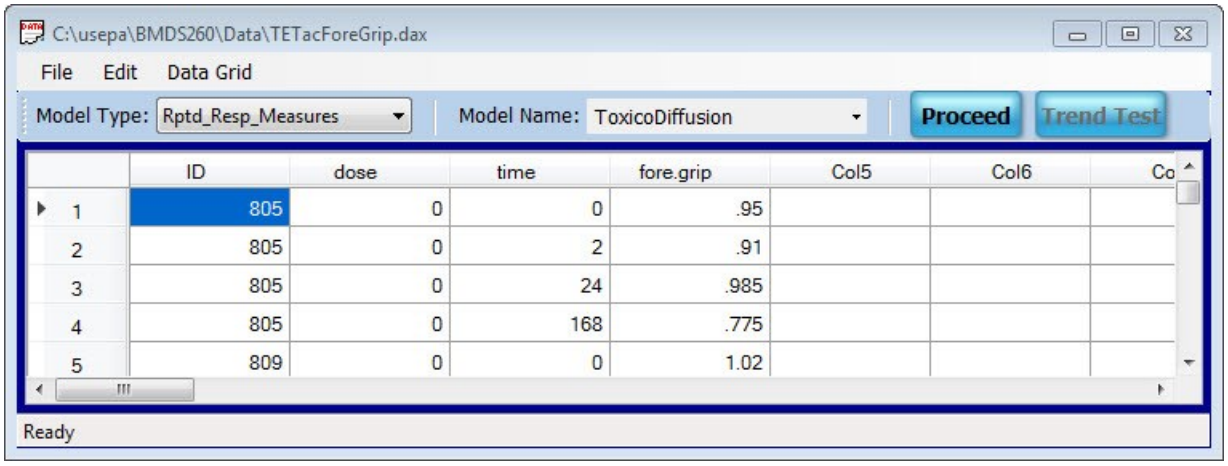
- Nested Models—Descriptions
- Nested Models—Text Output

REPEATED RESPONSE MEASURES OPTION SCREEN

After a dataset has been created and saved with a name that is not "Untitled," the user can initiate a repeated response measures analysis.

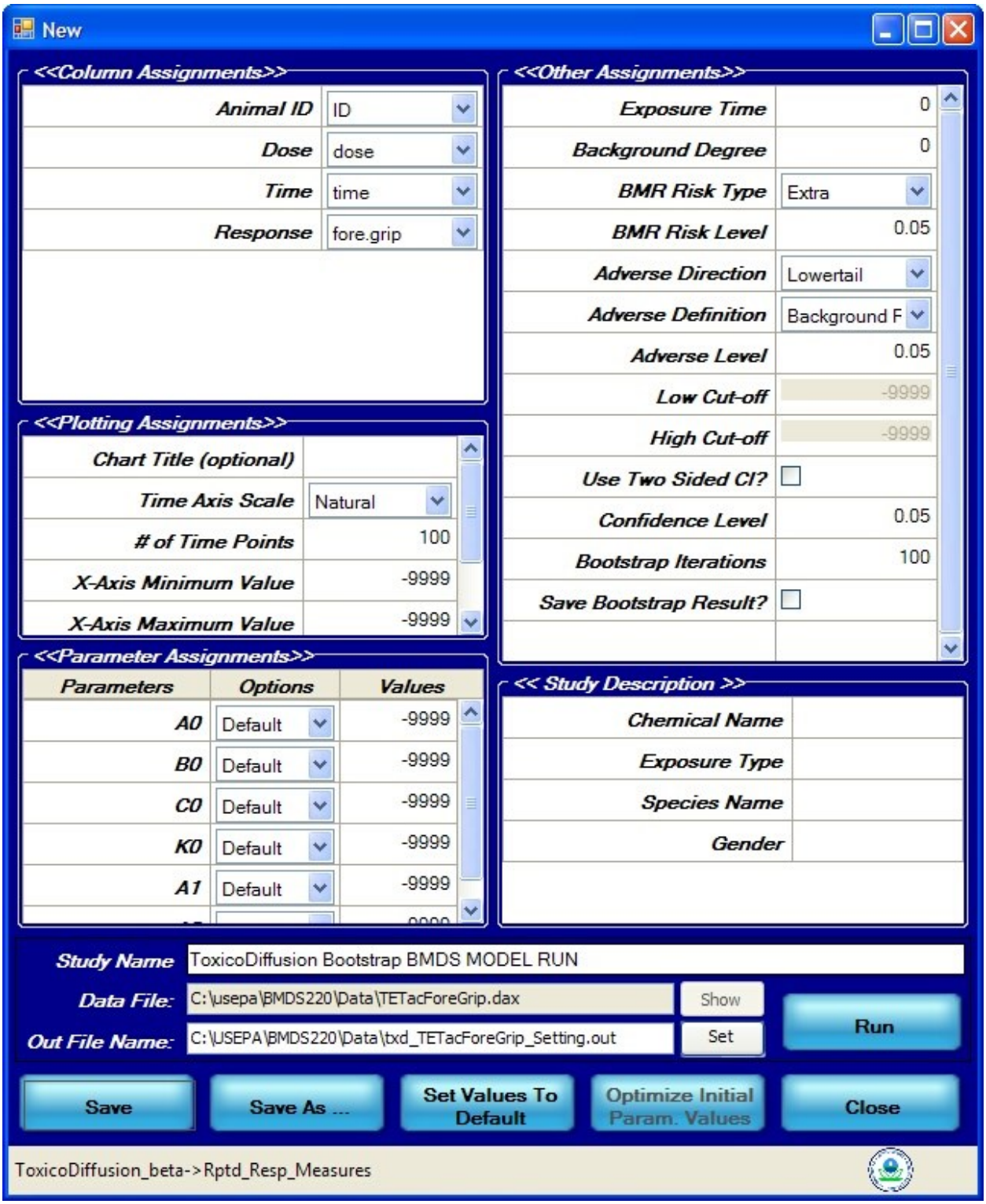
From the Data Grid window's Model Type field, select "Rptd_Resp_Measures" from the dropdown list and click **Proceed**. Note that currently ToxicoDiffusion is the only model of this type, so no model selection needs to be done. The ToxicoDiffusion model includes graphical outputs showing the observed and model-predicted time-course data, residuals, and a summary of the bootstrap-based BMDL calculations.

An example dataset for use with the Repeated Response Measures model is shown in the following figure:



The data for such an analysis will consist of one or more measurements from any given experimental unit (animal) at different times before or after the exposure. Thus, the dataset must include a column that identifies which animal the observations come from (the "ID" column in the above figure). Even though it is assumed that each animal is exposed to only one dose level, each row of data must include the dose value; the column assignment for that dose value is specified as shown above. The time of each observation (row) must be given (the "time" column) and the value of the response at that time must be recorded (in the "fore.grip" column). You will specify these columns in the Option Screen's Column Assignments section.

Clicking on **Proceed** opens a special Option Screen specifically designed to facilitate modeling with the Repeated Response Measures model:



This Option Screen is very similar to that for other BMDS models, so the following information will focus on its unique aspects.

Plotting Assignments

Identify the properties of the resulting graphs here.

Parameter Assignments

This section allows the user to either:

- Enable the program to find initial values for the optimization runs (the default values of “-9999” shown in the option screen are merely flags to pass to the input file that indicate this default option—they are not real initial values), or
- Initialize the parameter values to values of the user's choice (the “Initialize” option). Currently, the Repeated Response Measures model does not allow users to specify values of the model parameters.

Other Assignments

This section lets the user define other important components for the analysis. The time at which exposure occurs (time zero in many experiments) must be specified. So too must the user specify the background degree, which is an integer between 0 and 2 that determines how the responses are assumed to vary over time in the absence of exposure. This background (without-exposure) variation is defined by a polynomial of the specified degree (constant, linear, or quadratic for the choices 0, 1, or 2, respectively).

Adverse responses can be defined in one of two ways. Either a background rate of adverse response is specified (e.g., a 5% rate of adverse response in the absence of exposure) or cut-off value(s) can be specified, with the assumption that values above or below (depending on the adverse direction) the cut-off(s) are adverse. The background rate of response need only be defined of the definition is in terms of background rate (probability) of response; the cut-off(s) need only be defined if the definition is in terms of cut point(s).

“Other Assignments” also allows the user to specify the number of bootstrap iterations to run to estimate confidence bounds. As shown in the example screen above, those bounds can be one-sided or (if the “Use Two Sided CI?” box is checked) two-sided.

The number of bootstrap iterations should be large enough to provide a stable estimate of the bounds. The Bootstrap Iteration value shown above (100) is almost certainly too low for a final, stable estimate of those bounds. Values on the order of 100 or more will probably be required in most cases; the user should perhaps do several runs to determine that the bound estimates have stabilized for the number of iterations chosen. Increasing the number of iterations will noticeably increase the time it takes to run the model.

Note For "Confidence Level" the user must actually enter a p value such that the level of confidence is (1-p)*100%. For example, in the example screen above, the "Confidence Level" field has the value 0.05. This corresponds to requesting 95% confidence limits: (1—0.05)*100% = 95%.

Study Description

Here, the user can supply any additional experiment-specific information that s/he wished to have reported in the output files.

Running the model

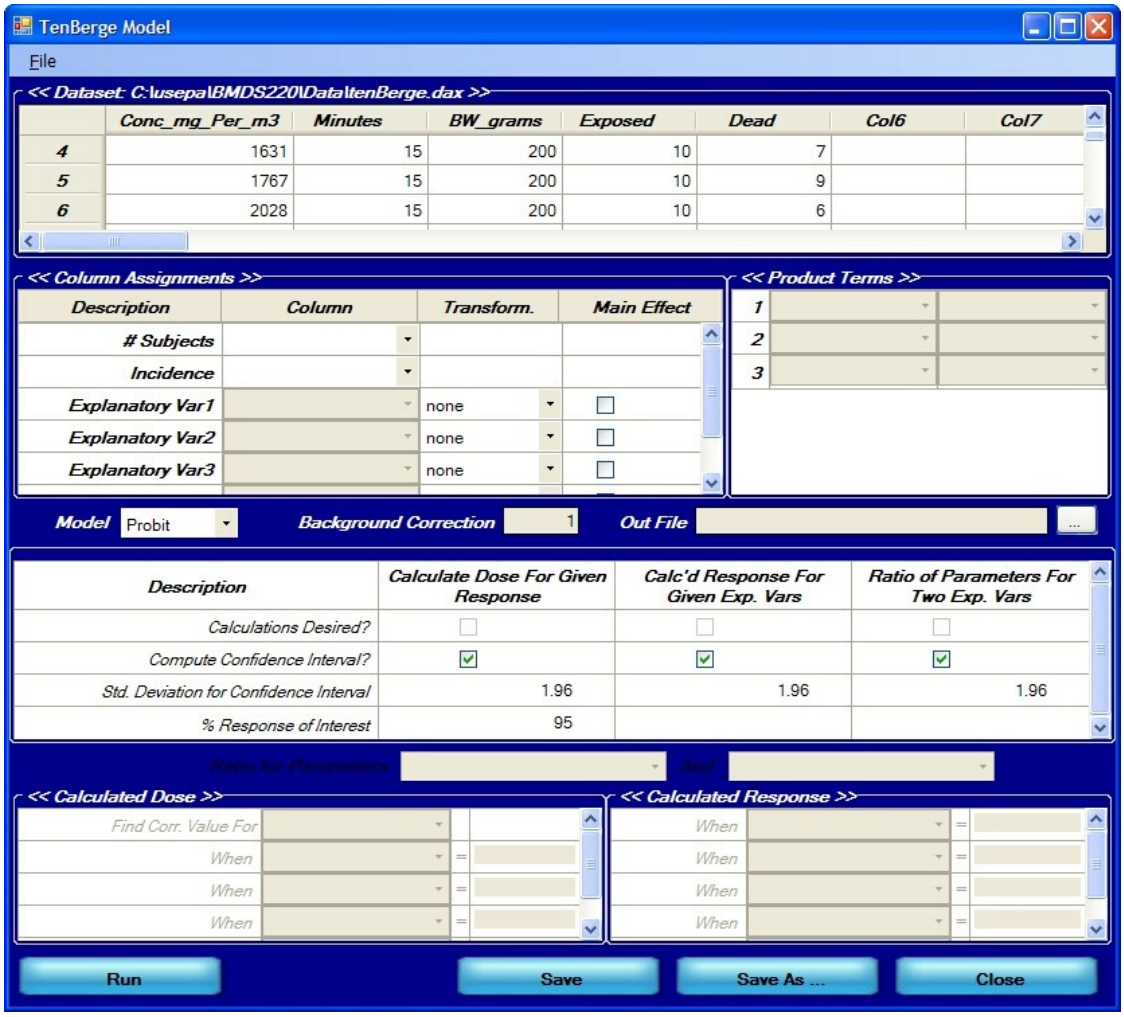
Once all the options have been specified as desired, clicking the **Run** button will initiate the repeated measures analysis. The run will produce a set of five graphs that will flash momentarily on the screen. When the run is complete, the full set of five plots will be available in a summary plot screen. The individual plots can be copied and pasted into other files (such as a Word document file).

See also:

- Repeated Response Measures Model Options Fields
- Repeated Response Measures Model Text Output
- Repeated Response Measures Model Description

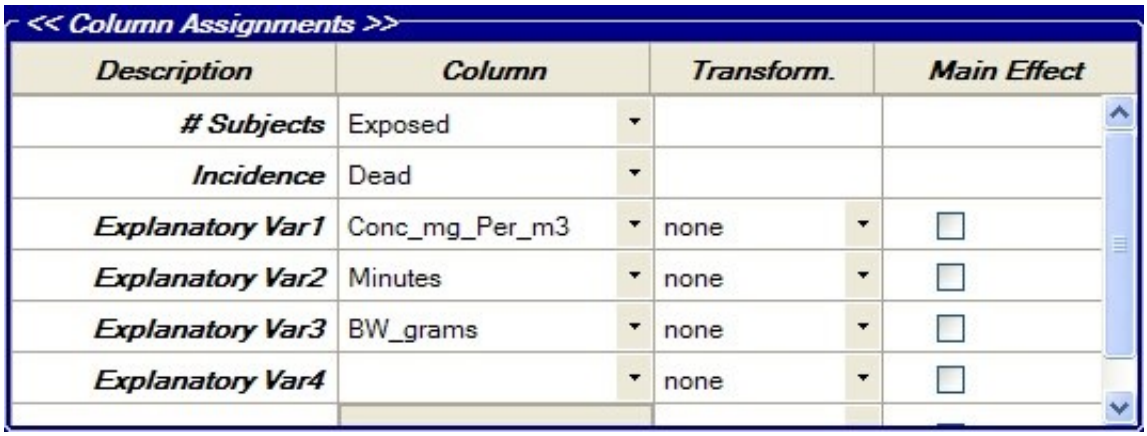
CONCENTRATION X TIME MODEL OPTION SCREEN

The option screen for analysis of Concentration x Time (CxT) data is a bit different from the option screens for other BMDS models, reflecting differences in the types of analyses they implement.



When first opened the only portion filled in is the top of the Option Screen, which displays the data from the dataset that was used to open this screen (along with the file path for the saved dataset). This top portion is for display of information only; it cannot be edited from this screen. Any changes to the data must be made on the Data Grid window, from which this option screen was created.

The data should include a variable corresponding to the number of subjects in each group ("Exposed" in this example) and the incidence in each group ("Dead" in this example). When the user fills in those two choices in the Column Assignments section of the screen, the remaining column names will automatically appear as possible explanatory variables (Explanatory Var1, etc.):

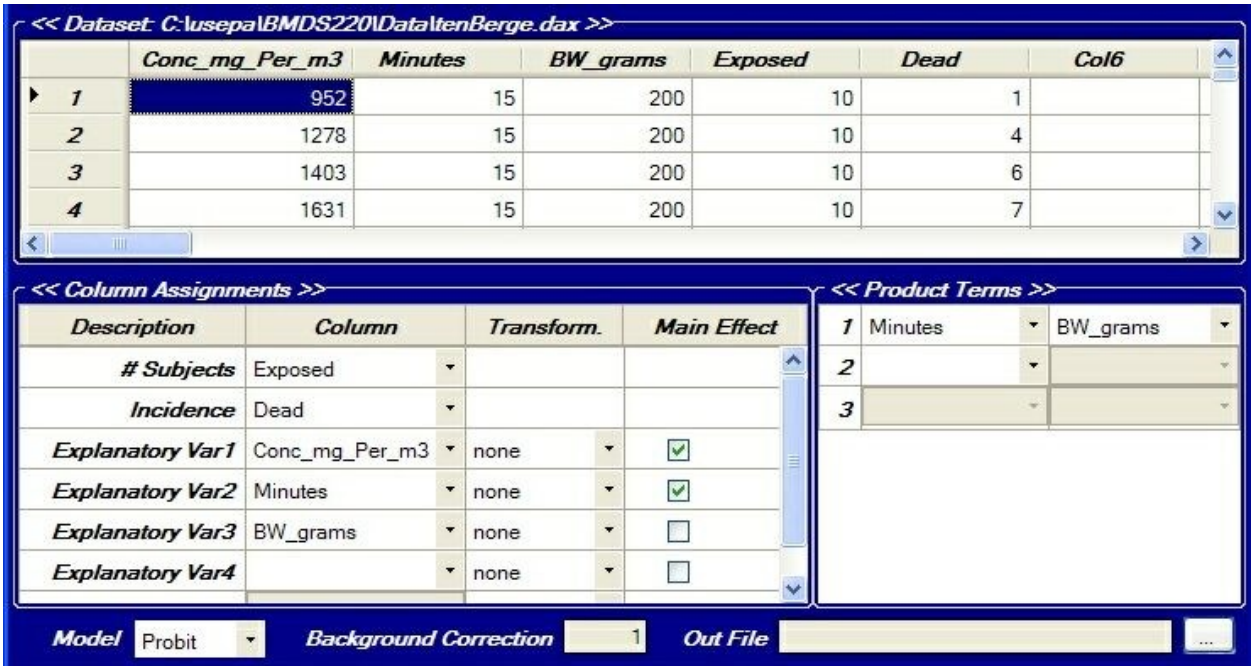


Currently, there is a limit of five possible explanatory variables. There must be at least two possible explanatory variables to run the Concentration x Time model; if there is only one possible explanatory variable, the user does not need the Conc_x_Time model—a standard dose-response model for dichotomous data (Dichotomous or Dichotomous_Alternative model types) will suffice.

One way (typically, the primary way) for a possible explanatory variable to be included in the model is as a main effect (it enters the model as a “stand-alone” independent variable. For a possible explanatory variable to be used as a main effect, the box under the “Main Effect” column must be checked for that particular explanatory variable. Not all of the possible explanatory variables need be included in the model as main effects.

After selecting the explanatory variables to be included as main effects, the user can then define up to 3 product terms to be included in the model. Note that explanatory variables included as main effects need not be in the product terms,

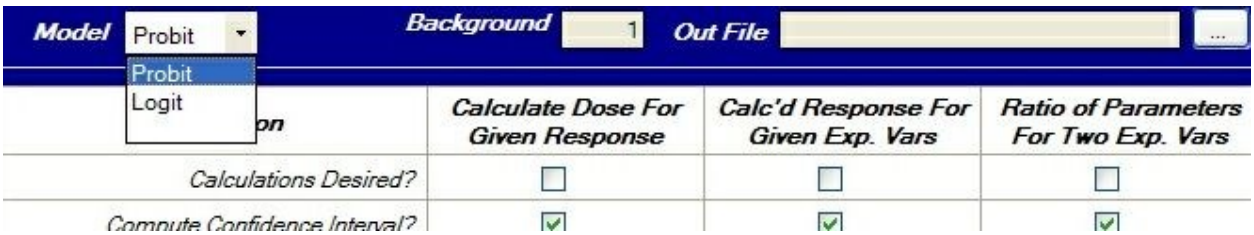
and conversely, the product terms need not be restricted to explanatory variables included as main effects. One example is shown in the following screenshot:



Note that explanatory variables 1 and 2 are selected as main effects (but variable 3 is not). Also note that a product term is being selected for inclusion in the model; this product term consists of variable 2 (a main effect) and variable 3 (not a main effect). Therefore, this model would contain 2 main effects and 1 product term.

The variables can be used as is or they can be transformed. The transformations currently available are the logarithmic (y = Ln(x)) and the reciprocal (y = 1/x) transformations. Whatever transformation is chosen will be used everywhere that variable occurs in the specified model (main effect and any product terms). The three transformation choices are accessed for each variable from the drop down list in the “Transform.” column to the right of the variable name.

A logit or a probit model may be selected as the basis for the concentration-time modeling from the drop down menu for the “Model” field just below the Column Assignments:



In the above screen shot, note that there is a (disabled) option for a background correction. Because that option is disabled, all Concentration x Time models currently run in BMDS will not have a background response correction.

The user has the option of specifying the name of the output file that will contain the results of the run. A name can be selected by clicking on the " . . ." button to the right of the grayed out "Out File" name field. **DO NOT** enter a name in that grayed out field. Click the " . . ." button and a window will appear showing the contents of the last file where BMDS files were accessed (the Data folder under BMDS if you have just opened BMDS). Navigate from there to the place you want to save the output file, and enter a name of your choice in the "File name" field of that window. That name and its associated path will then appear in the option screen "Out File" field. **REMEMBER**, as always in BMDS, the output file name (and the folders in the path to it) **should NOT have spaces** in the name.

At this point, the model can be run to completion and parameter estimates obtained. This would suffice to allow estimation of all parameters needed for generating plots (via the Excel tool that implements two graphing options; see Graphic Output from Models in this documentation for more information). However, if the user wants more information reported in the model output file, additional selections can be made as described below.

The user may specify what additional types of estimates are desired; there are three choices as indicated in this screenshot of the lower portion of the CxT option screen (any or all of the choices may be selected):

Note that in the above screen shot, much of the lower portion of the option screen is inactive (grayed out) because, at this point, no additional calculations have been requested.

The three options for additional calculations are discussed in the following sections.

Options for Additional Calculations

- Option 1—Calculate Dose for Given Response
- Option 2—Calculated Response for Given Explanatory Variables
- Option 3—Ratio of Parameters for Two Explanatory Variables

See also:

- Concentration x Time Data
- Concentration x Time Model Description
- Concentration x Time Model Text Output

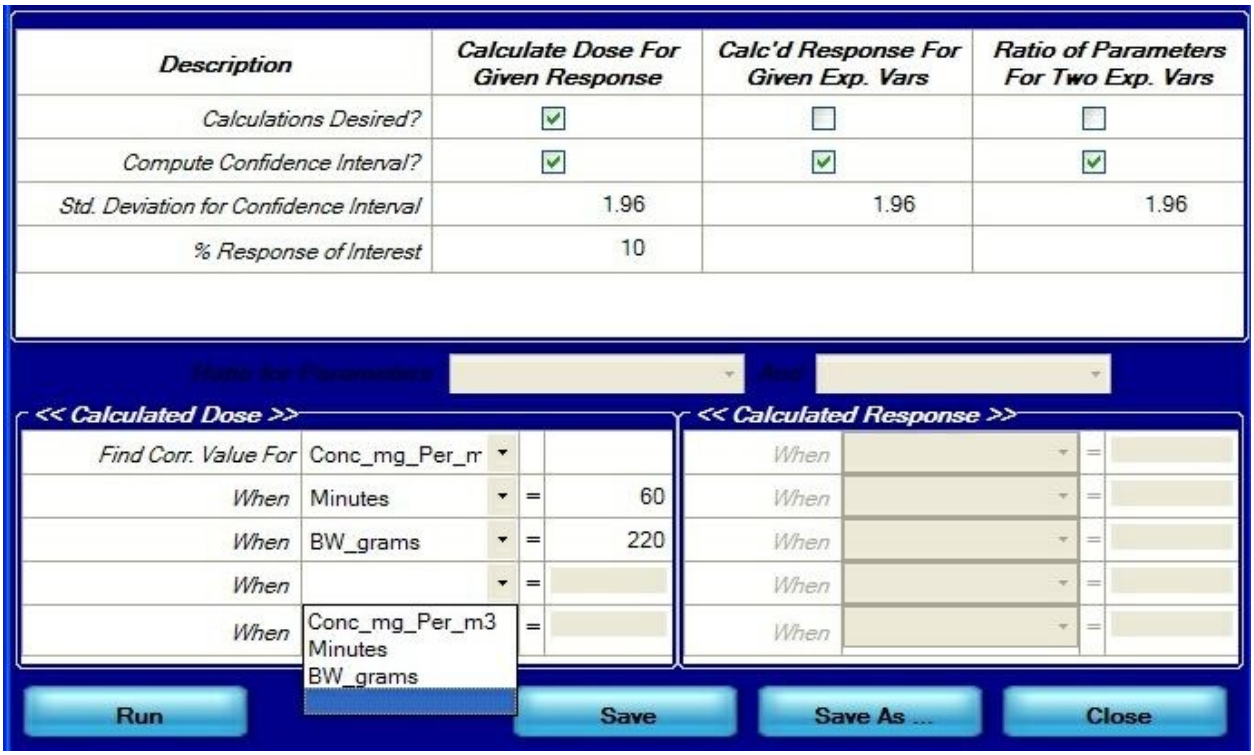
Option 1—Calculate Dose for Given Response

A BMD type of calculation would correspond to the choice “Calculate Dose for Given Response” where the user specifies a response level (as a percent strictly between 0 and 100, e.g., 95 as in this example) and then requests the value for one of the explanatory variables included in the model (usually dose or concentration) when the other explanatory variables are set to specific values. To obtain such estimates, check the box (by clicking on it) in the “Calculations Desired?” row for the “Calculate Dose for Given Response” column.

Note When that box is checked, the **Run** button will no longer be active (it will be grayed out) because the user needs to provide additional information in the “Calculated Dose” section in order for the calculation to succeed. (The same is true when the other options for additional calculations discussed below are requested.)

Also (here and in the following two options for additional calculations), the fields in which the user specifies the input needed for the requested calculations will be grayed out until and unless the corresponding “Calculations Desired?” box is checked.

The following screenshot shows how to access the variable choices for the required fields (that have not become active because the "Calculations Desired?" box is checked) via the drop down lists in the "Calculated Dose" section:



In this case, the model will calculate what concentration of exposure will result in a 10% response when time = 60 minutes and body weight = 220 grams.

Note The estimates provided in the output will not be valid unless all explanatory variables used in the model (as main effects or in one or more product terms) are listed either in the row "Find Corr. Value For" (the variable one wants to calculate) or have been set to a value in one (and only one) of the "When" rows.

The "Std. Deviation for Confidence Interval" can be determined from Table 22. Note that this approach was used here because one might often be using a value from a t-distribution rather than a normal distribution. Refer to Concentration x Time model for additional information.

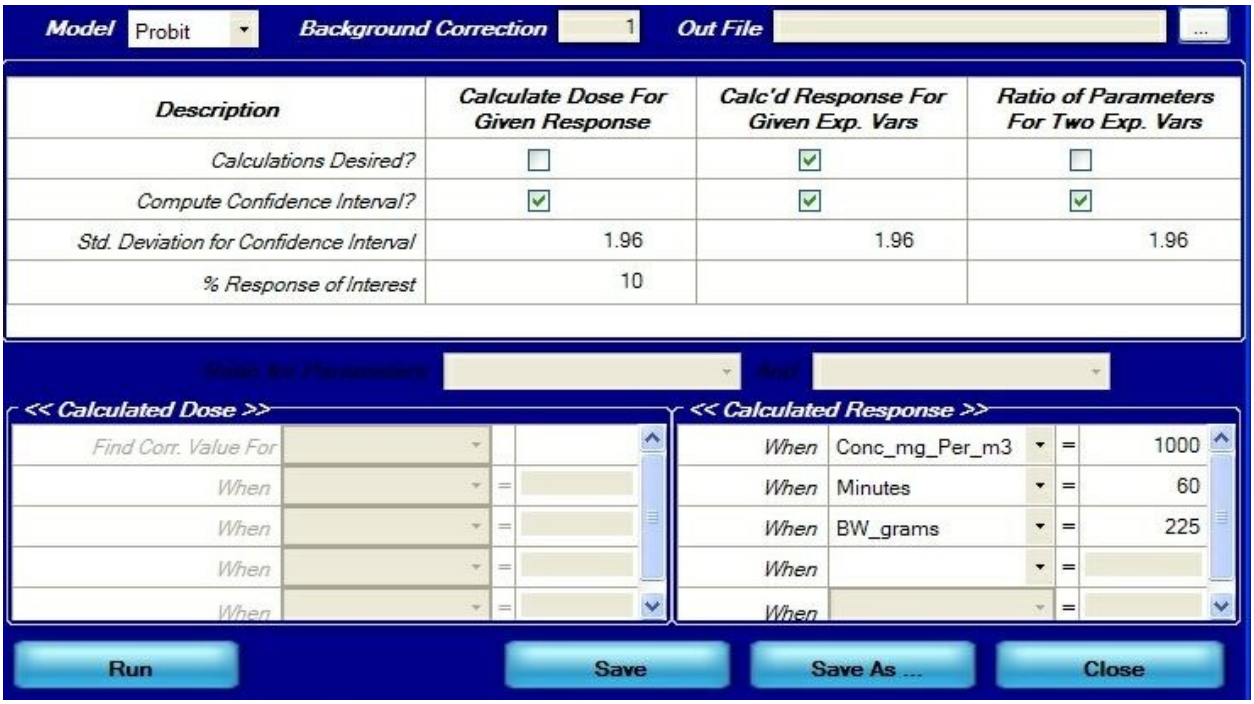
Table 22: *Deviates corresponding to confidence levels of interest for confidence interval estimation (from standard normal distribution)*

α	Confidence Level	Deviate
0.2	80%	1.282
0.1	90%	1.645
0.05	95%	1.960
0.01	99%	2.576

The user can determine the deviate to use for other confidence levels of interest from a table of quantiles of a standard normal distribution, available in many elementary statistics books (or s/he may compute them using Microsoft Excel function "NORMSINV" and putting in (1-?/2) as the argument to that function when interest is in the 100*(1-?) confidence interval).

Option 2—Calculated Response for Given Explanatory Variables

The user can also calculate the response level expected when all of the explanatory variables (the ones included as main effects or in product terms) are at specified values; s/he does so by choosing "Calc. Response for Given Exp Vars" (i.e., by checking the box in the "Calculations Desired" row under that column). In the following screenshot, the user has requested that the output report the probability of response when exposure is to 1000 ppm, for 60 minutes, for an animal weighing 225 g.



The std deviation to input when confidence interval calculations are requested are the same as above for the "Calculate Dose" request.

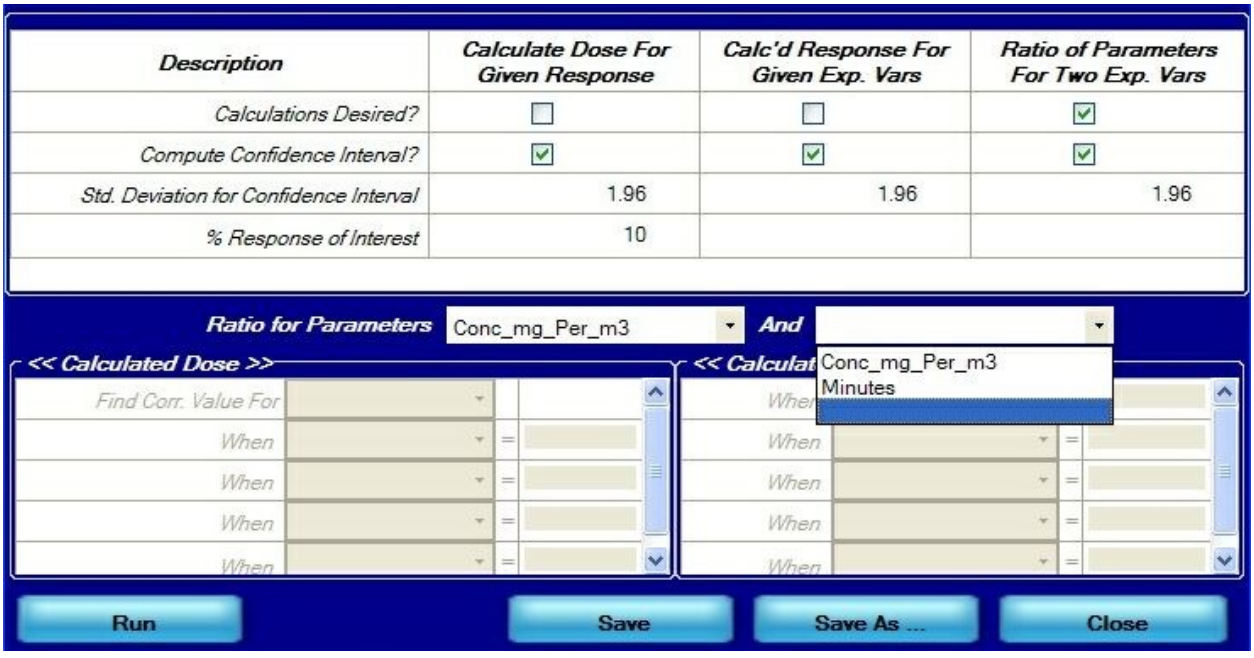
> ***Note*** The estimates provided in the output will not be valid unless each explanatory variable used in the model (as main effects or in one or more product terms) is listed and given a value in one (and only one) of the "When" rows in the "Calculated Response" section of the screen.

Option 3—Ratio of Parameters for Two Explanatory Variables

Finally, the user may calculate the ratio of the parameters of two main effects by choosing "Ratio of Parameters for Two Exp. Vars". This ratio is often considered when concentration and time are logarithmically transformed, as a measure of "n," which is the slope of the response contours on the Ln(conc)-Ln(time) plots.

As in the previous two requests for additional calculations, the user indicates that such estimates are desired by checking the box in the "Calculations Desired?" row in the "Ratio of Parameters for Two Exp. Vars" column. Then the cells corresponding to the remaining required fields will no longer be grayed out and values must be entered for all such fields in order to run the model.

The following screenshot shows that the user has requested the ratio of the coefficients for Conc_mg_Per_m3 and Minutes.



The above example also shows how to access the parameters for desired main effects via the drop down lists. Those lists will only include variables that have been included in the model as main effects.

The choices of std deviation for confidence interval calculations are the same as for the “Calculated Dose” options.

Warning

In this example, and any other example where product terms involving either concentration or time are included in the model, the ratio of the parameters for the main effects of concentration and time will not have the interpretation given above (i.e., it will not be the slope of the contours on a log-log plot), even if the logarithmic transformation has been chosen for those variables. In fact, with product (interaction) terms, those contours would, in general, not be straight lines.

Once a Concentration x Time modeling option screen has been completed, it may be saved using the “Save” or “Save As . . .” buttons on the screen. The extension for a Concentration x Time model run is “.ten” and should be used for all such saves. If the user wants to revisit a saved Concentration x Time model analysis, the “Open” option under the File menu item can be used to do so (see How to Use BMDS/Concentration x Time Data).

WORKING WITH SESSION AND OPTION FILE TEMPLATES

Versions 2.1 and higher of BMDS come with templates for sessions and option files that the user may find helpful for facilitating the creation of sessions suitable for analyzing his or her data. The user can “swap in” any data (.dax) file for use with these templates as long as the data file is structured correctly.

The following sections describe those templates and the types of analyses for which they may be most useful.

In the SessionFiles folder (located at C:\Usepa\BMDS230\Data\SessionFiles for BMDS 2.3.1), the user will find several templates with the following naming convention:

XXX[-other descriptive information].ssn

Within that convention, XXX is one of the following:

XXX = Dichotomous,
Cancer,
Continuous,
NestedSample, or
Dichotomous_AlternativeSample

corresponding to the 5 main categories of dose-response models included in BMDS (excluding Concentration x Time models and Repeated Response Measures models, which differ in that they are designed for analyses of multiple

explanatory variables or multiple observed responses per experimental unit, respectively).

The second part of the template naming conventions, "-other descriptive information," describes more specific characteristics of the templates, as explained in the next sections

DICHOTOMOUS MODEL SESSION TEMPLATES

The templates for the Dichotomous model sessions include every dichotomous model, including the Dichotomous Hill model, but excluding the multistage-cancer model (because it is a special case of the multistage model and is included in its own templates—see the "Cancer" template description below) and all the Dichotomous_Alternative models (which also have their own template). The template names for the Dichotomous models include two further identifiers and so have the form Dichotomous-YYY-ZZZ.ssn.

The "YYY" part of the name specifies the BMR level. For example, "BMR01" designates that all the model options for that session are set up to estimate the BMD and BMDL corresponding to 1% extra risk. Templates with "BMR05" and "BMR10" are set up to calculate BMDs and BMDLs corresponding to 5% and 10% extra risk, respectively.

The "ZZZ" part of the name is either "Restrict" or "Unrestrict" and specifies whether estimated parameters in the models (e.g., slope, power or polynomial coefficients) are restricted or unrestricted, respectively. In some instances, the restrictions avoid numerical computation problems. In all but one case where the option to restrict exists, restricting model parameters is the EPA default approach. This typically keeps the estimated models from assuming biologically unrealistic patterns (e.g., such as infinite slopes for very low doses or nonmonotonicity). The one exception is the LogProbit model, which has a slope parameter that can become very steep, but does not approach infinity, at very low doses.

Note For this reason, a risk assessor should report the results of an unrestricted LogProbit model run along with the results from a session of restricted models.

CANCER MODEL SESSION TEMPLATES

The templates available for running a session on a cancer endpoint have the naming convention "Cancer-BMRxx.ssn." The "xx" is one of "01," "05," or "10," indicating that the BMD and its bounds are calculated for extra risks of 1%, 5% or 10%, respectively.

There are no restrictions to specify with the cancer model because, by definition, the multistage-cancer model has the coefficients restricted to be non-negative. These sessions fit the multistage cancer model with three different polynomial degrees (first degree through third degree).

There is a session template named “Cancer-AlternativeSample.ssn” that fits the multistage-cancer-BgDose (background dose) model to a dataset. Like the “Cancer-BMRxx.ssn” templates, it fits a first degree, second degree, and third degree polynomial model to a dataset. The BMR is set to 10% extra risk.

CONTINUOUS MODEL SESSION TEMPLATES

There are several templates that are set up to run all of the continuous models in BMDS. The templates available for running a session of continuous models designate not only the definition of the BMR and restrictions, but also the form of the variance model and the direction of the change in mean response. In two instances, the names indicate that the data are entered in the form of individual responses (a value recorded for each experimental unit) as opposed to the more typical summary data (means and standard deviations) that are assumed for all the other templates.

Thus, as an example, the session template

Continuous-ModelVariance-BMR1Std-Up-Restrict.ssn

specifies that all the models will be run with modeled variance (the other alternative is constant variance), with a BMR defined as a change in the mean equal to 1 (control group) standard deviation, with the assumption that the means are increasing as a function of dose, and with the parameters of the models restricted (when that applies for any given model). The template

Continuous-ModelVariance-BMR1Std-Up-IndividualResponses-Restrict.ssn

implements the same set of models with the same options, except that it would be used if the data were entered as individual (experimental-unit-specific) dose and response values.

The other continuous model session templates allow estimation of the BMD corresponding to 10% or 5% change in the mean (“BMR10” or “BMR05” in the third part of the template name, respectively). There are also templates that accommodate data with decreasing means (“Down” in the fourth part of the name).

OTHER MODEL SESSION TEMPLATES

The NestedSample.ssn and Dichotomous_AlternativeSample.ssn templates are set up to run all models within the type specified (Nested or Dichotomous_Alternative, respectively) on dataset(s) that the user may specify. As "sample files," there are no variations with respect to restrictions or BMR definitions. All the option files used in those sessions restrict parameters (when that is relevant to the model in question) and calculate BMDs and BMDLs corresponding to 10% extra risk. The user may create sessions implementing other options (e.g., with respect to restrictions or BMR level) by making changes to the option files, analogous to the way in which the Dichotomous model template variations were defined above and modifying the Option files as described next.

OPTION FILE TEMPLATES

The session templates described above implement the options that are associated with them (e.g., BMR level) through specifications of the model options in the Option Files that are included in those session templates. The Option File templates are found in the "OptionFiles" folder in the "Data" folder within the folder in which BMDS was installed.

Like the session templates, the Option File templates have names reflecting the options that have been selected. But, because the Option Files are model-specific, the templates for the Option Files begin with a three-letter abbreviation designating the model to which the Option File corresponds. The list of model abbreviations can be found on the Model Abbreviations page.

Thus, the Option file template names begin with the three-letter abbreviation appropriate to the model under consideration in lieu of the model type that begins the session template names. The other parts of the Option File template names correspond to the choices listed above for the session template names, specifying choices for the BMR, restriction of the parameters, variance model, etc. For example, the template

Dhl-BMR10-Restrict.opt

is for the dichotomous Hill model ("dhl" is the abbreviation for that model), with the benchmark response level set to 10 percent extra risk, and with the slope restricted (to be greater than or equal to 1 in the case of the dichotomous Hill model). It is one of the option files used in the Dichotomous-BMR10-Restrict.ssn template (i.e., the option file for the dichotomous Hill model run in that session). Similarly,

Pow-ModelVariance-BMR05-Restrict.opt

is for the continuous Power model ("pow" is the abbreviation for that model), with the variances modeled, the benchmark response level set to 5% change in the mean, and the power parameter restricted to be greater than 1.

USING THE TEMPLATES

The user may use the templates as the basis for quickly setting up sessions to run some standard types of analyses. For example, if s/he wishes to run all the dichotomous models on some (dichotomous) noncancer endpoint, using the EPA defaults, s/he would open

Dichotomous-BMR10-Restrict.ssn.

Then s/he would choose or create the dataset of interest and change the entry in each row under the "Data File" column of the session screen so that that entry has the name of the dataset of interest.

ALIGNING VARIABLE NAMES WITH DATA GRID COLUMN NAMES

The Option File templates for Dichotomous, Dichotomous_Alternative, and Continuous model types are set up with standardized variable names for each model. If the user creates or uses a dataset with the following Data Grid column headers for each of those variables, then it is not necessary to edit the option files in the session templates.

The default column headers for the variables used in the BMDS models are described in .

Table 23: *Default column headers for model variables*

Model Variable	Column Header
Dose (independent variable)	Dose
# Subjects in Dose Group (sample size)	N
Incidence (# responders)	Effect [dichotomous models]
Mean	Mean [continuous models]
Standard Deviation	Std [continuous models]
Individual Response	Response [continuous models]

It is also important to note that if other variable names (column headers) are used in the dataset or column headers renamed in the Data Grid, then ***the Option files will have to be edited*** (see Step 4: Specify Model Parameters) so

that the column assignments section of the Option screen shows the correct names (column headers).

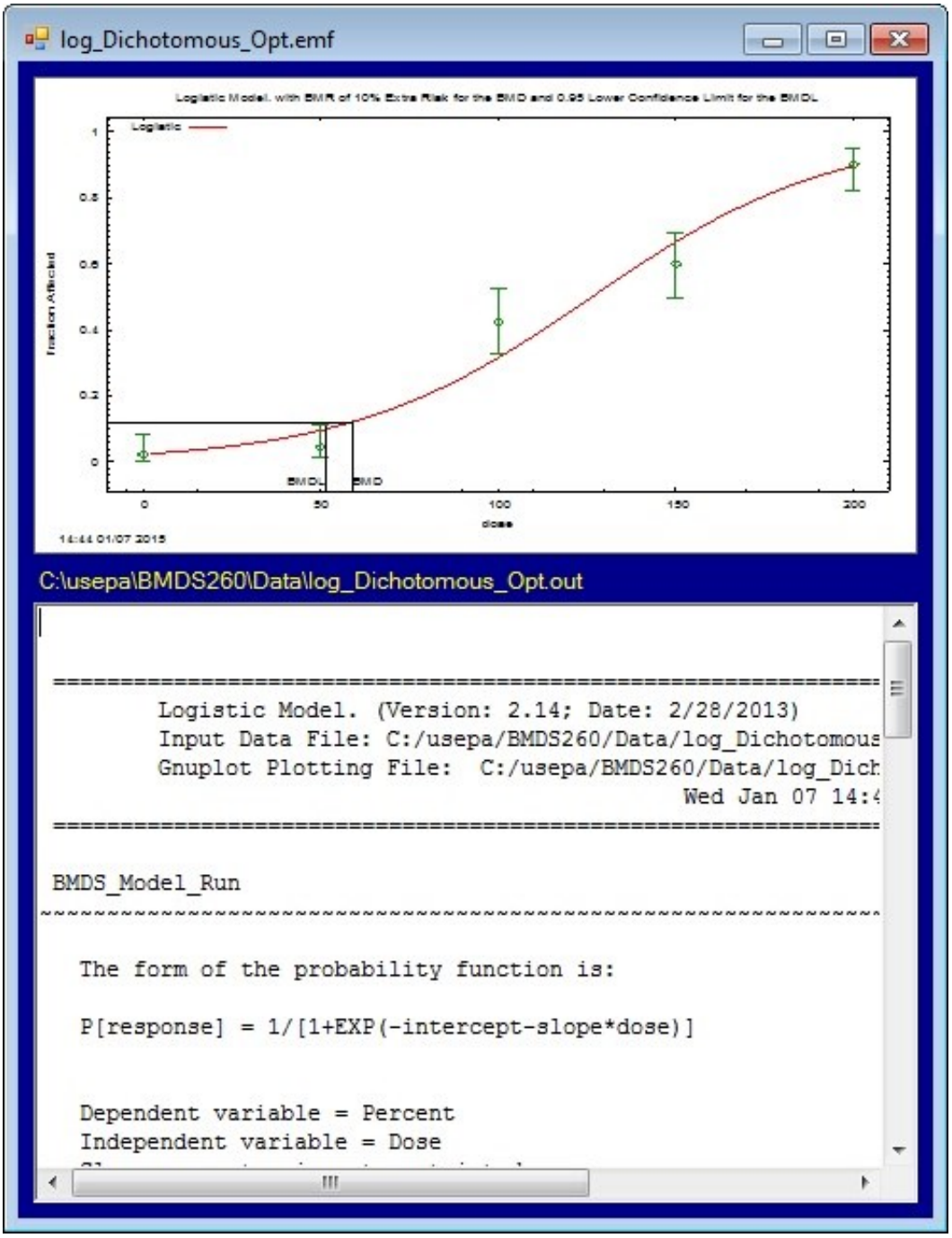
See also:

- Step 3: Create or Import a Dataset
- Step 4: Specify Model Parameters
- Renaming Columns
- Model Option Screens
- Model Abbreviations

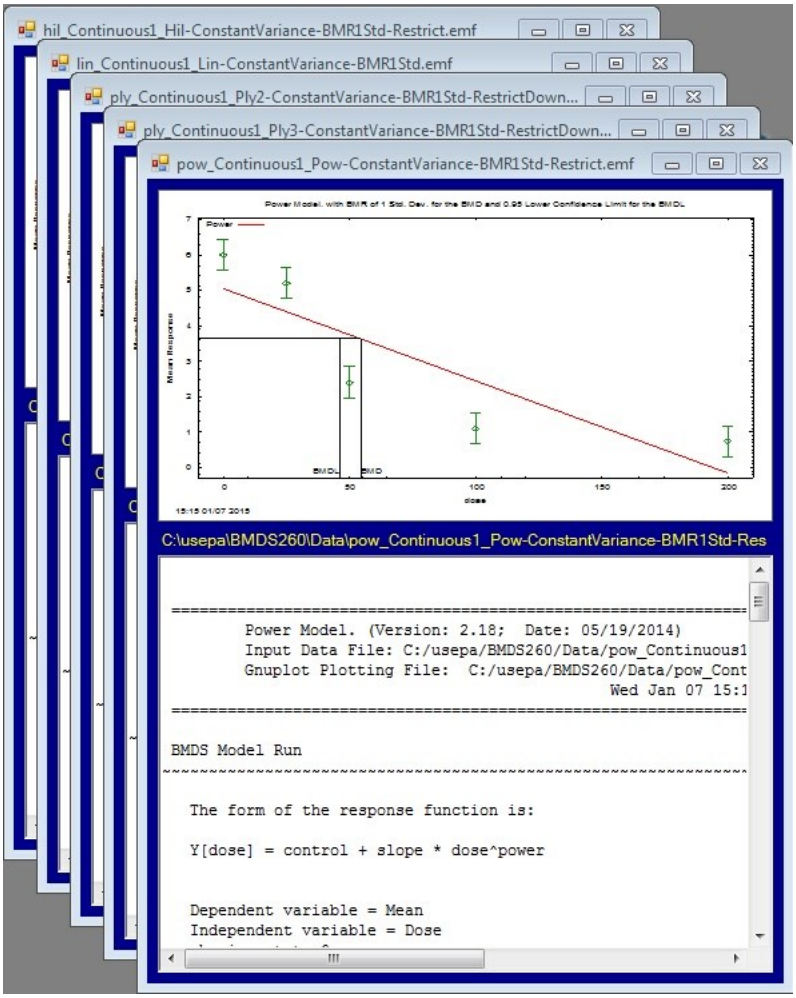
WORKING WITH REPORTS AND OUTPUT

After you have specified all the pre-requisites (models, data, parameters) for a session run, click the **Run** button in the bottom left of the Session Grid window. The Session Grid's status bar will display a “Please wait processing . . .” message and a progress bar as BMDS calculates the results.

A result consists of a plotted graph for the model plus its Out File data display. The following screenshot shows an example of an individual graph and Out File data display.



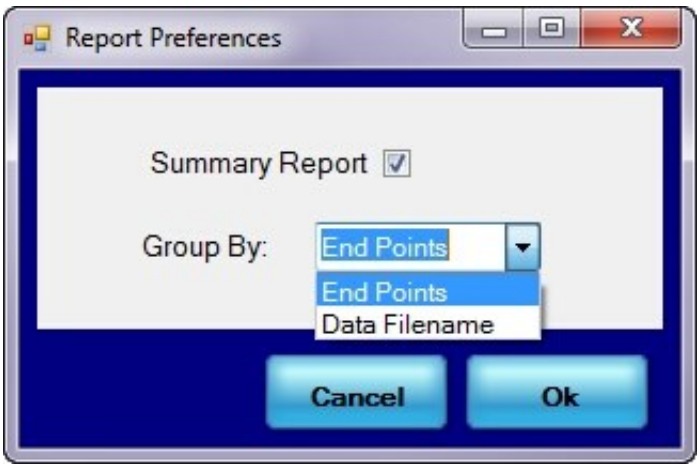
You can choose whether to display each model's report and graph individually or to group them into Summary Reports and Summary Graphs windows. If you include several models in your session run, then viewing each model's run individually can lead to stacked windows, as shown in the following example.



Using the summary windows, you can review multiple results more easily from a single window display. The Summary Report Window collects the results into a single tabular format, while the Summary Graphs Window collects the graphs into a single window.

SETTING REPORT PREFERENCES

1. From the BMDS menu bar, select Tools>Preferences …>Report to display the following dialog box:



2. Choose from the options described in Table 24.

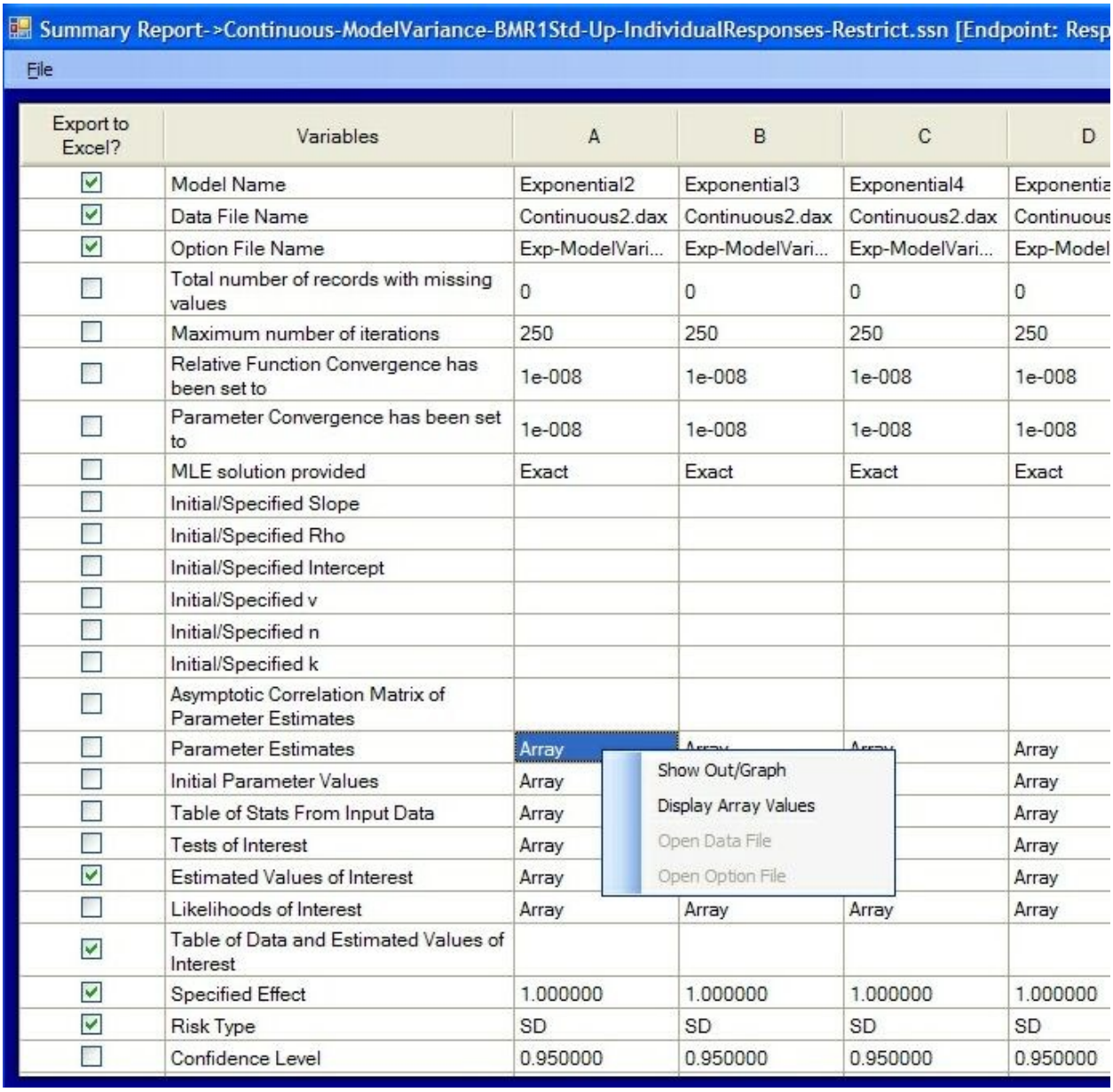
Table 24: *Report Preferences options*

Option	Description
Summary Report	A checkmark to the right of this option (default) indicates a summary report and summary plots will be displayed after a session run. If unchecked, the summary report is not generated and plots are displayed in separate windows.
Group By	This option determines how session run results (summary reports and summary plots) are grouped together. Results can be grouped by end points (default) or by the data file name

WORKING WITH THE SUMMARY REPORT WINDOW

If the "Summary Report" option has been selected under the **Tools > Options** menu, the results will be displayed in two new windows: a textual Summary Report and a Summary Graph.

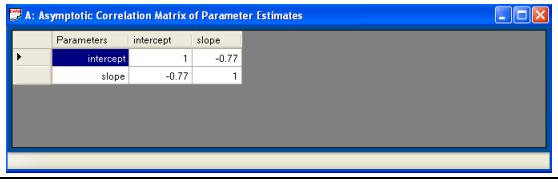
The Summary Report window displays the variables set for each of the models run in a tabular format. Each lettered column corresponds to the models previously added in the Session Grid window.



Export to Excel?	Variables	A	B	C	D
☑	Model Name	Exponential2	Exponential3	Exponential4	Exponentia
☑	Data File Name	Continuous2.dax	Continuous2.dax	Continuous2.dax	Continuous
☑	Option File Name	Exp-ModelVari...	Exp-ModelVari...	Exp-ModelVari...	Exp-Model
☐	Total number of records with missing values	0	0	0	0
☐	Maximum number of iterations	250	250	250	250
☐	Relative Function Convergence has been set to	1e-008	1e-008	1e-008	1e-008
☐	Parameter Convergence has been set to	1e-008	1e-008	1e-008	1e-008
☐	MLE solution provided	Exact	Exact	Exact	Exact
☐	Initial/Specified Slope				
☐	Initial/Specified Rho				
☐	Initial/Specified Intercept				
☐	Initial/Specified v				
☐	Initial/Specified n				
☐	Initial/Specified k				
☐	Asymptotic Correlation Matrix of Parameter Estimates				
☐	Parameter Estimates	Array			Array
☐	Initial Parameter Values	Array			Array
☐	Table of Stats From Input Data	Array			Array
☐	Tests of Interest	Array			Array
☑	Estimated Values of Interest	Array			Array
☐	Likelihoods of Interest	Array	Array	Array	Array
☑	Table of Data and Estimated Values of Interest				
☑	Specified Effect	1.000000	1.000000	1.000000	1.000000
☑	Risk Type	SD	SD	SD	SD
☐	Confidence Level	0.950000	0.950000	0.950000	0.950000

Right-click in any lettered column to display a context menu with the options described in Table 25.

Table 25: *Summary Report Window context options*

Option	Description
Show Out/Graph	Display individual graphs and Out File data for the selected model.
Display Array Values	To display array values, right-click on a cell containing the word "Array." The following screenshot shows an example of an array values window. 
Open Data File	Display the data file linked to the displayed results.
Open Option File	Display the option file linked to the displayed results.

EXPORT SELECTED SUMMARY REPORT ROWS TO EXCEL

If you want to perform more detailed analysis on specific results displayed in the Summary Report Window, you can easily export those rows to Excel.

The Summary Report window pre-selects some rows for export, which you can easily change.

Export to Excel can export results for sessions containing any number of models.

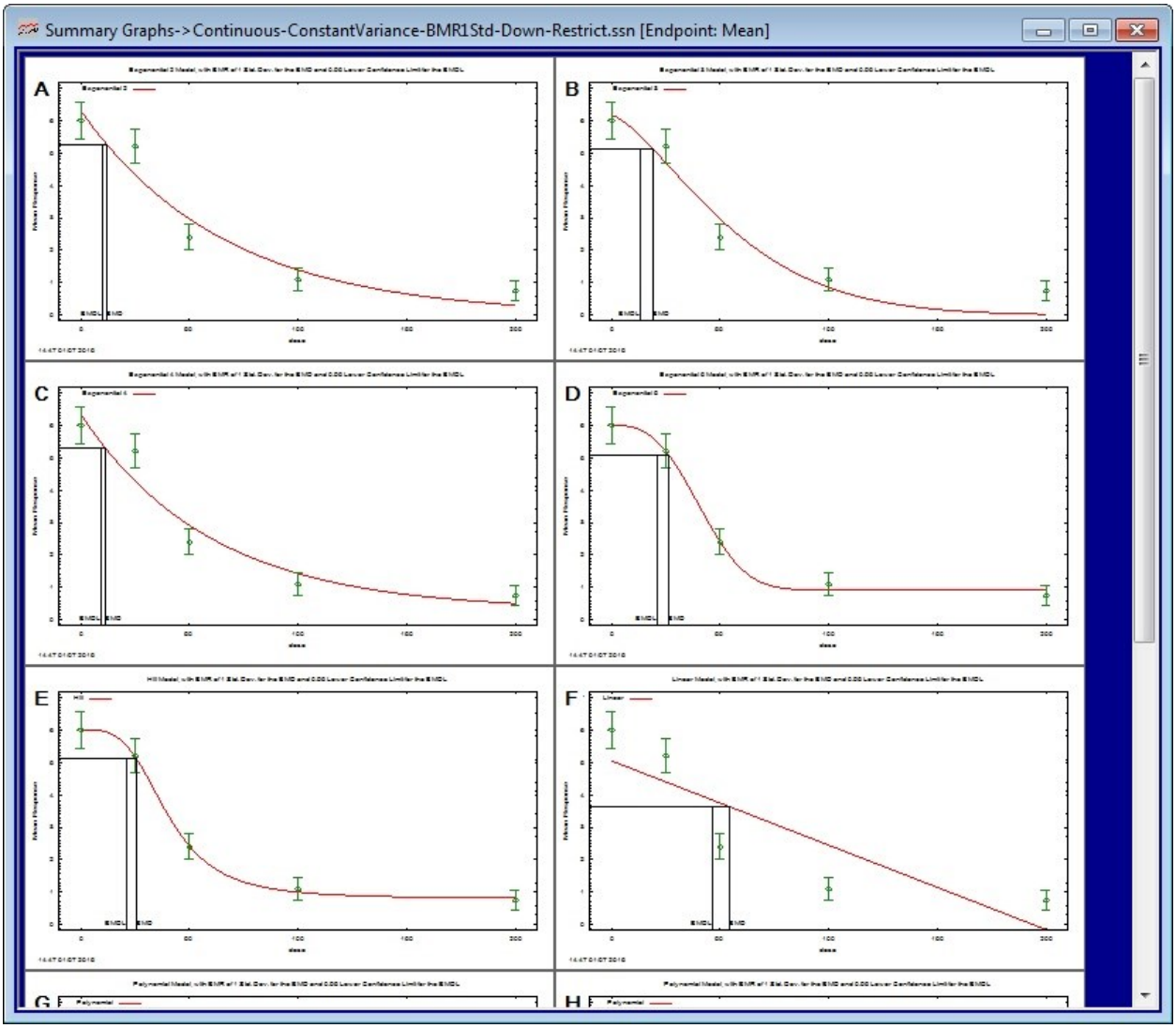
1. In the Summary Report window, check the boxes in the Export to Excel? column to select those rows for export.
2. From the Summary Report window's menu bar, select **File>Export to Excel**.

An Excel window will open, create individual tabbed worksheets within a new Excel workbook, and enter and format the data. The new workbook contains data only from the rows selected.

Individual worksheet tabs include Plots, Inputs+Estimates+Scaled Res., and other tabs, depending on the model type.

SUMMARY GRAPHS WINDOW

The Summary Graphs window displays graphs corresponding to each model run. Right-click on individual graphs to copy them to the clipboard; you can then paste them into other files, such as Microsoft Word documents.



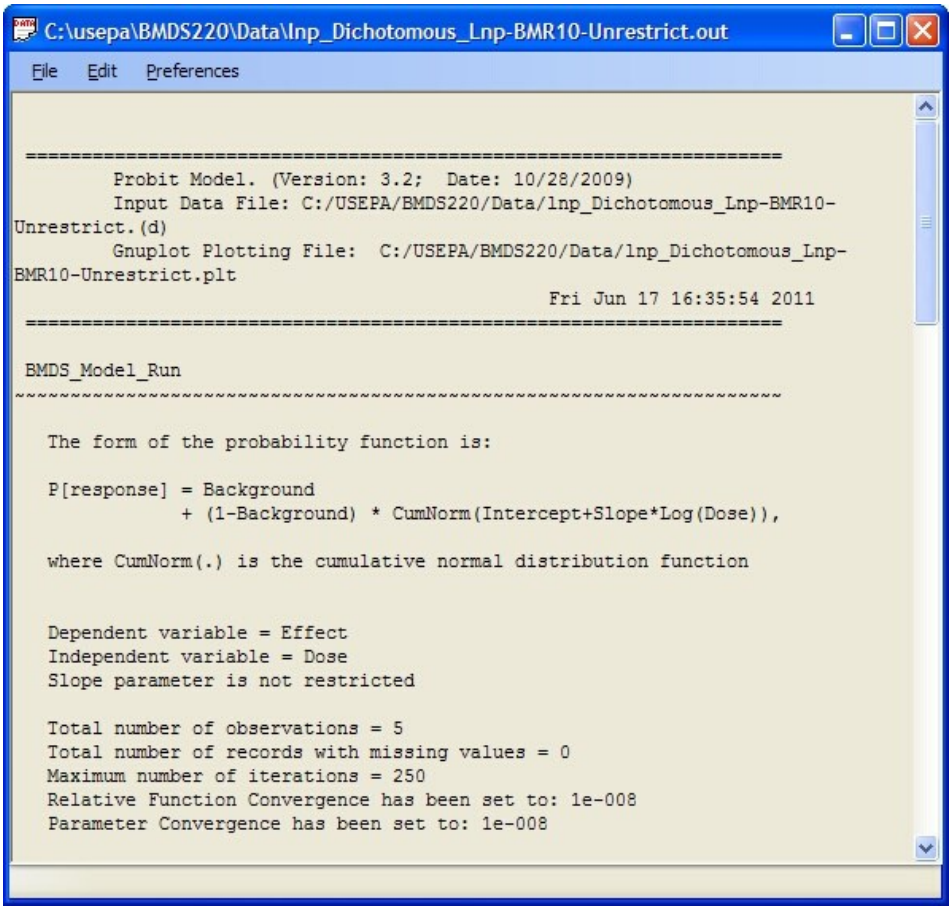
VIEWING OUTPUT (.OUT) FILES

The text output file has the extension "*.out". Out files are saved to the BMDS application directory's Data subdirectory (for example, BMDS240\Data).

The Out file is a simple text file you can open using Notepad or BMDS.

Displaying the output file

1. From the BMDS menu bar, select **Tools>View Output File …**BMDS displays in the Open dialog box all the .out files in the Data subdirectory.
2. Locate and select the .out file you wish to view and click **Open**. The Out File is displayed in the BMDS text window.



VIEWING PLOTS

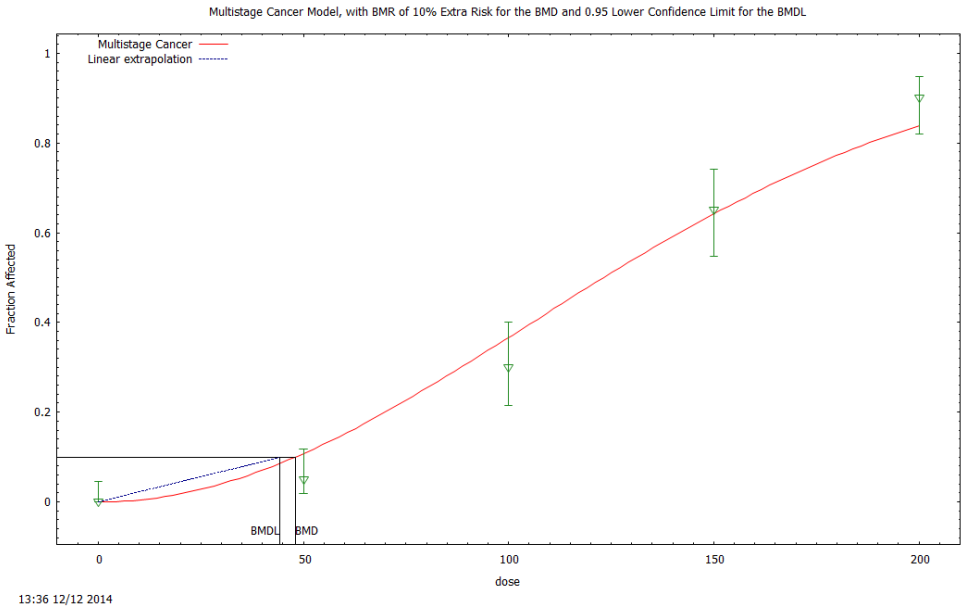
The plot (*.plt) file that serves as the basis for the graph is located in the BMDS Data subdirectory (for example, BMDS240\Data). The .plt file will have the same filename as the *.emf and *.out files in the output window.

So, for example, the *.plt file for pro_Dax_Setting.emf, would be pro_Dax_Setting.plt.

Plot files are displayed using GnuPlot, an open-source application included as part of the BMDS install package.

Displaying plots

1. From the BMDS menu bar, select **Tools>View Plot File …**BMDS displays in the Open dialog box all the .plt files in the Data subdirectory.
2. Locate and select the .plt file you wish to view and click **Open**. The plot is displayed as a GnuPlot graph in its own window.



- The BMD and BMDL are identified on the plot as black vertical lines and are associated with the response level associated with the user-selected BMR, the horizontal black line.
- The BMD curve estimated by the model is represented by a red line.
- Data points are shown in green with their individual group confidence intervals.

See Also:

Using GnuPlot

USING GNUPLOT

BMDS includes GnuPlot as part of the standard installation. GnuPlot is an open-source, command-line driven graphing utility that can run on multiple operating systems. GnuPlot offers many editing and customization features you may find useful when transforming the plots for use in reports or other media.

You can modify the graphic display features by using either GnuPlot's edit features or copying the plot to the Windows clipboard and pasting it into another application capable of performing vector graphic editing (e.g., Microsoft PowerPoint).

You can access copy and edit features in GnuPlot by left-clicking on the small graphic icon at the top of the plot page or right-clicking on the graph. A menu will appear with options to modify the plot window in various ways.

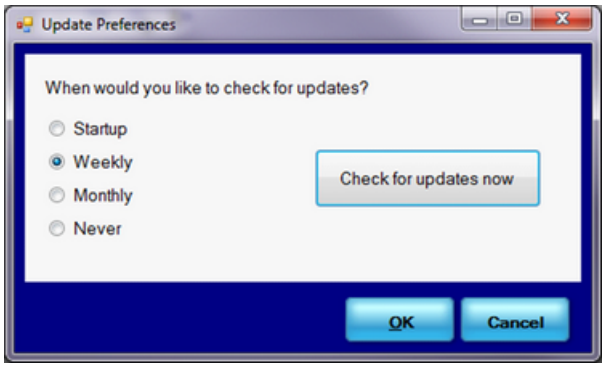
Among the options available are:

- Copying to the clipboard
- Changing the background color
- Specifying different colors, line styles (solid, dash, line widths, etc.), and fonts
- Specifying printing options, such as landscape or portrait

For more information, please refer to the GnuPlot homepage.

KEEPING BMDS UP TO DATE

After you start BMDS, and assuming your computer has an Internet connection, the software will check the BMDS server for any updates. You can change the frequency of this check using the **Tools>Preferences>Update** dialog box:



From this dialog box, you can select whether BMDS checks for a new update:

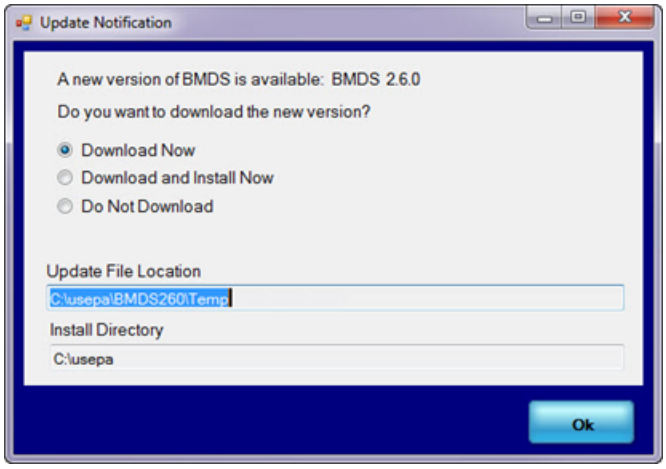
- On startup
- Weekly (the default)
- Monthly

You can also choose to manually check for updates by selecting Never and clicking the **Check for updates now** button.

Note that BMDS ***must be running*** so it can check for and notify you of an update.

WHEN AN UPDATE IS READY FOR DOWNLOAD

When BMDS detects that an update is ready to download, it will display the following dialog:

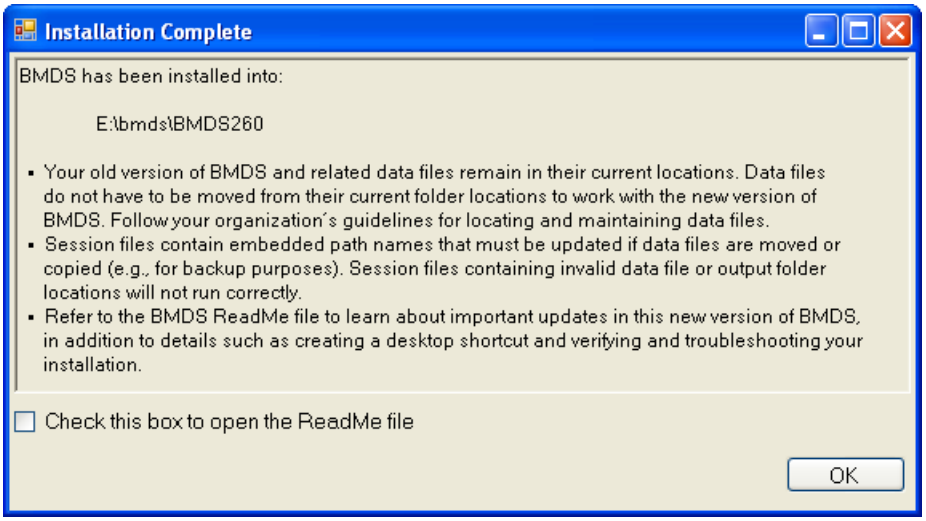


You can choose the following options:

- To download the update and install it yourself later (the default)
- To have BMDS download and automatically install the update. The dialog shows the Update File Location where BMDS will download the new update file and the Install Directory where the new BMDS directory will be created if automatically installed. These fields are read-only and cannot be edited; BMDS enforces this information to ensure a stable installation process.
- To not download the update

If you choose to download and install the software yourself, you can follow the instructions described in the BMDS readme file included with the install package. The manual installation process is unchanged from previous BMDS releases.

If you choose to have BMDS automatically download and install the update, then BMDS displays the following information box after installation:



Note that this automatic install process is done under your user account and does not require a system administrator.

Tick the box and click OK to view the BMDS readme file. Your computer will need a PDF reader to view the readme file.

TO USE THE NEWLY INSTALLED BMDS SOFTWARE

Following an automatic installation, the older BMDS version does not shut down; it remains open.

To use the newly installed BMDS software:

1. Close the old BMDS version.
2. Review the readme file to learn about new features, bug fixes, or other need-to-know items regarding the new software.
3. Follow the instructions in the readme file to:

- Create a shortcut for the new BMDS version on your desktop
- Determine that the new BMDS version works properly on your computer
- Fix possible issues with displaying the help file

MANAGING YOUR EXISTING MODEL INPUT AND OUTPUT FILES AFTER AN AUTOMATIC UPDATE

- The automatic BMDS install does not replace or displace your existing model input and output files. Your old version of BMDS and related data files remain in their current locations. Data files do not have to be moved from their current folder locations to work with the new version of BMDS. Follow your organization's guidelines for locating and maintaining data files.
- Session files contain embedded path names that must be updated if data files are moved or copied (e.g., for backup purposes). Session files containing invalid data file or output folder locations will not run correctly.

TROUBLESHOOTING

HELP FILE DOES NOT DISPLAY

Some users have reported that clicking or double-clicking on a Help topic generates the message "Navigation to the web page was canceled."

Solution: change the security permission for the help file—BMDS*.chm—to "Full Control." If you're unable to change the permission, then you will need to work with someone who has Administrator rights to make this change.

To change the permission:

1. Right-click on the BMDS*.CHM file in Windows Explorer and select "Properties" from the context menu. The Properties dialog box appears.
2. Click the "Security" tab.
3. In the Permissions box at the bottom, click to place a check mark in the "Allow" column for "Full control."

DECIMAL AND THOUSANDS SEPARATORS IN BMDS

BMDS 2.6 supports regional settings for the decimal separator in the user interface and in spreadsheets created by the Export to Excel function.

However, you should be aware of BMDS's treatment and presentation of decimal separators and thousands (or "digits") separators in the user interface and in data files:

- No "thousands separator" (regardless of regional setting) can be used in the data; that is, one thousand can only be written as 1000 rather than as 1,000.

- Files generated by BMDS (such as the .out files and .d files) will still show a period (“.”) as the decimal.
- The Data Grid will convert/display an opened .dax file from “.” or “,” as the decimal separator to the specified decimal separator set by the Control Panel's Region and Language settings.
- The Model Options screens will display and read values using the specified decimal separator.

AVOID USING WINDOWS-RESERVED CHARACTERS IN FILE AND PATH NAMES

BMDS allows any character, except for Windows reserved characters, to be used when naming files or directories that BMDS will access.

However, the following Windows reserved characters are still disallowed and cannot be used:

< (less than)

> (greater than)

| (vertical bar or pipe)

? (question mark)

* (asterisk)

“ (double quote)

Note The backslash (\) should be used when specifying network drive paths.

PATH+FILENAMES SHOULD NOT EXCEED 255 CHARACTERS

The combination of path and filename for BMDS data and output files cannot exceed 255 characters.

BMDS can be installed either locally (on your workstation) or on a network drive.

A local path is structured in the following order: drive letter, colon (:), backslash (\), and name components separated by backslashes. The total of all those characters should not exceed 255.
Example: **`C:\usepa\BMDS260`**

The path for UNC (network) path names can be structured as: *ComputerName**ShareName**Path*. The total of all those characters should not

exceed 255.
Example: `\\FileSrv1\Users\JDoe\USEPA\BMDS260`

When path names exceed the 255-character limit, BMDS may experience such problems as being unable to open a document, run a model, or terminate unexpectedly.

Workarounds include shortening the name of the file or one or more directories containing the file, or moving the file to a directory with a shorter path.

REQUEST SUPPORT WITH ETICKET

For any technical problem related to running BMDS, please select **Help>BMDS Support**. This will display the eTicket site in your default web browser, where you can request help, ask a question, or check on the status of an existing issue.

BMDS BEST PRACTICES

The following sections describe various procedures or processes that will make your BMDS sessions more productive, accurate, and reliable for obtaining optimal model convergence.

OPTIMIZATION CRITERIA

The default optimization criteria (Relative Function Convergence and Parameter Convergence) are set to 1e-8, meaning that successful convergence is determined if the relative change in the function value and the change in the parameter values from one iteration to the next are less than 1e-8. It has been noted on a very few occasions that those criteria may not be adequate.

So, when using BMDS, if you note a particularly poor model fit (especially when other models do seem to fit the data relatively well), you may want to try changing the convergence criteria to 1e-10. This is not guaranteed to solve the problem, nor is this option available for all models. If the option screen for the model in question has an “Optimizer Assignment” section, then the criteria can be modified.

ALTERNATIVE DICHOTOMOUS MODELS

A set of alternative dichotomous models (most of which are “background dose” models) is available to the user.

When using BMDS, if the standard dichotomous models fail to provide an adequate description of the observed dose-response relationship, the user may want to explore the alternative models to see if any of them provide a satisfactory fit to the data.

RE-INITIALIZING PARAMETERS

BMDS models have internal logic for determining initial values for the parameter estimation. However, in some small fraction of cases, those calculated initial values may fail to provide an adequate starting point for the (global) maximization of the likelihood.

If the user suspects that the reported maximum-likelihood estimation (MLE) results are not satisfactory (e.g., the fit of the model is not good, while other models or user-supplied parameter estimates for the model in question appear to describe the data much better), then the user may find it useful to provide initial

values. The user-supplied initial values will supersede the model calculated values.

In fact, if the user wishes to try optimization from several starting (initial) points, then that would serve to enhance confidence in the results (if they all converge to the same MLEs).

The user can initialize parameters using the options in the Parameter Assignments section of the model option screens, changing the "Default" choice, under "Options," to "Initialized." If one parameter is initialized, all parameters must be initialized.

LOGNORMAL RESPONSE OPTION

When modeling continuous response data, the standard assumption for the BMDS continuous models is that the underlying distributions (one for each dose group) are Normal, with a mean given by the dose-response model and a variance as specified by the user (constant or a function of the mean response). An alternative assumption is that the responses are Lognormally distributed.

Currently, only the Exponential models allow the user to choose between Normal and Lognormal distribution assumptions. If the user has access to the individual response data, those data can be log-transformed prior to analysis. If the user suspects that the responses are Lognormally distributed, the best practice for now is to only use the Exponential models, with the Lognormal option for underlying distribution. The set of Exponential models covers a wide range of dose-response shapes and will be adequate in many modeling contexts.

Using log-transformed responses in the analysis is not recommended, for the following reasons:

- If you choose to log-transform the data prior to analysis, then the interpretation of the BMD and BMDL estimates would have to be considered carefully (and perhaps in consultation with a statistician). Data interpretation when using log-transformed responses will not be the same as when using the natural-scale response values. Indeed, the models—when "transformed back" to the natural scale—will not correspond to any of the standard BMDS models.

  For example, if using the power model on log-transformed responses, the user is actually implicitly modeling the medians (on the natural-scale) with the function $\exp\{\text{background} + \text{slope}*\text{dose}^{\text{power}}\}$ which is not a standard BMDS model and whose characteristics (e.g., exponential increases in response) may not be those desired by the user.

- Similarly, the interpretation of the BMD will not correspond to simple expressions (e.g., if the BMR is set equal to a relative deviation of 10%, that relative deviation will be assessed on the log-scale and so will not yield BMD or BMDL estimates that correspond to a 10% change in the original mean responses).

For these reasons, log-transforming the response values is not considered a "best practice" and, as stated, should only be applied and interpreted with supporting statistical expertise.

See also:

Continuous Model Descriptions

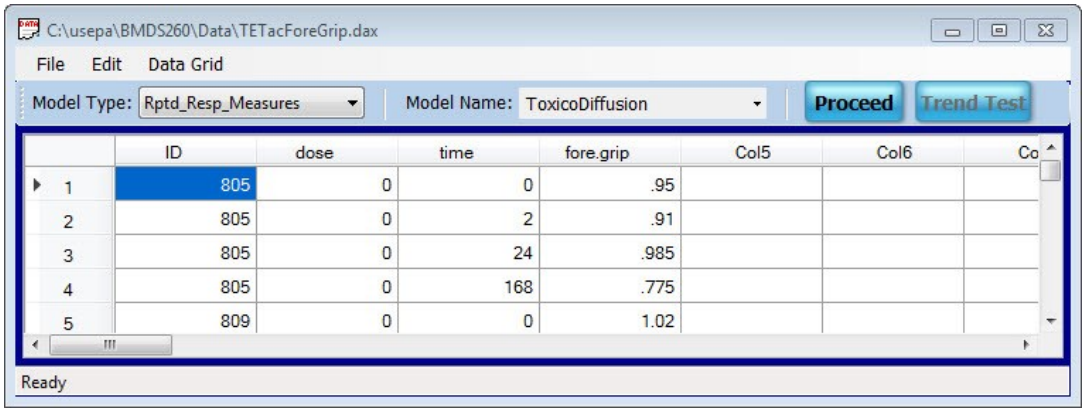
OTHER DATA OR ANALYSIS TYPES

REPEATED RESPONSE MEASURES

After a dataset has been created and saved with a name that is not “Untitled,” the user can initiate a repeated response measures analysis.

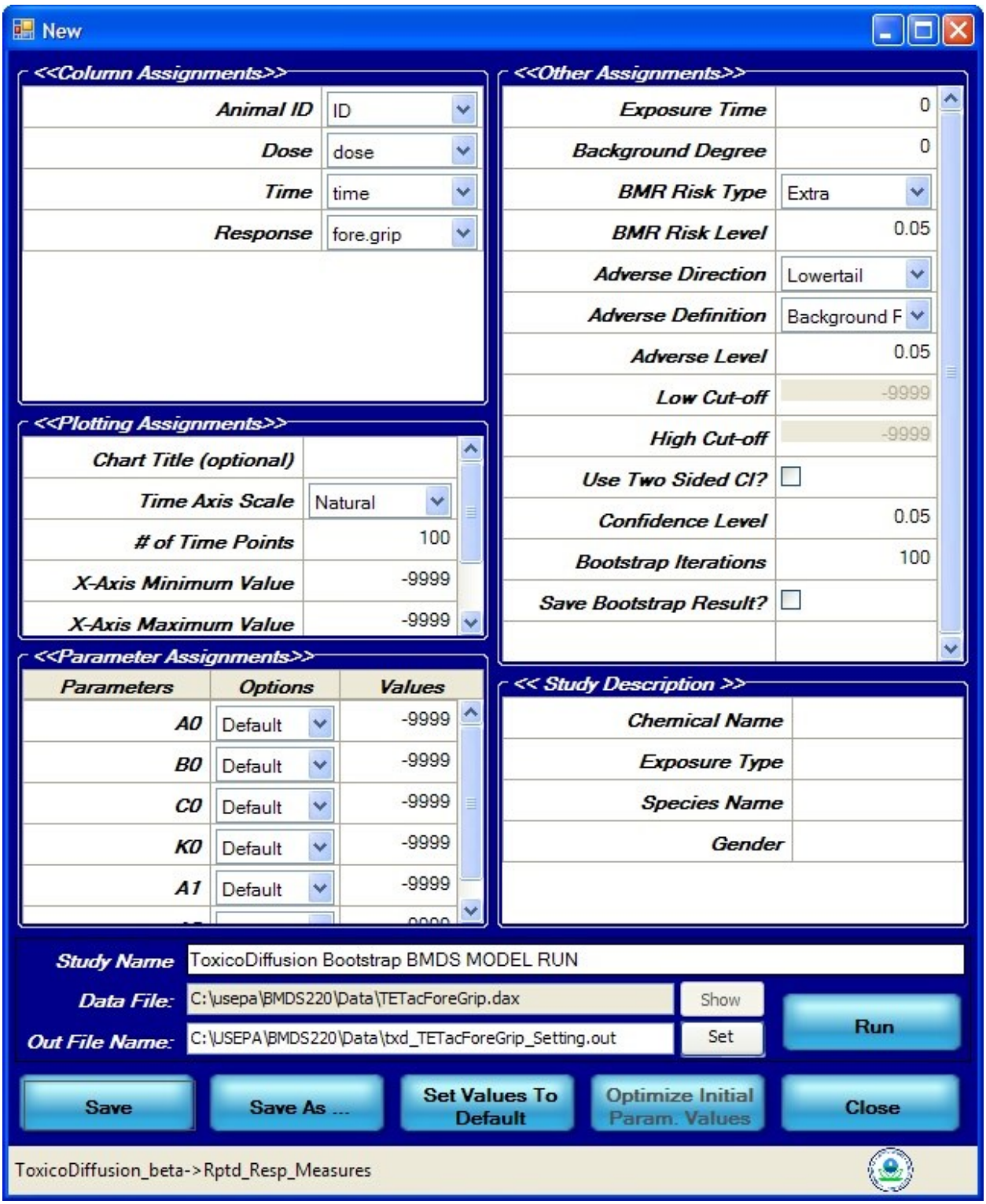
From the Data Grid window's Model Type field, select “Rptd_Resp_Measures” from the dropdown list and click **Proceed**. Note that currently ToxicoDiffusion is the only model of this type, so no model selection needs to be done. The ToxicoDiffusion model includes graphical outputs showing the observed and model-predicted time-course data, residuals, and a summary of the bootstrap-based BMDL calculations.

An example dataset for use with the Repeated Response Measures model is shown in the following figure:



The data for such an analysis will consist of one or more measurements from any given experimental unit (animal) at different times before or after the exposure. Thus, the dataset must include a column that identifies which animal the observations come from (the “ID” column in the above figure). Even though it is assumed that each animal is exposed to only one dose level, each row of data must include the dose value; the column assignment for that dose value is specified as shown above. The time of each observation (row) must be given (the “time” column) and the value of the response at that time must be recorded (in the “fore.grip” column). You will specify these columns in the Option Screen's Column Assignments section.

Selecting **Proceed** opens a special Option Screen specifically designed to facilitate modeling with the Repeated Response Measures model:



This Option Screen is very similar to that for other BMDS models, so the following information will focus on its unique aspects.

Plotting Assignments

Identify the properties of the resulting graphs here.

Parameter Assignments

This section allows the user to either:

- Enable the program to find initial values for the optimization runs (the default values of “-9999” shown in the option screen are merely flags to pass to the input file that indicate this default option—they are not real initial values), or
- Initialize the parameter values to values of the user's choice (the “Initialize” option). Currently, the Repeated Response Measures model does not allow users to specify values of the model parameters.

Other Assignments

This section lets the user define other important components for the analysis. The time at which exposure occurs (time zero in many experiments) must be specified. So too must the user specify the background degree, which is an integer between 0 and 2 that determines how the responses are assumed to vary over time in the absence of exposure. This background (without-exposure) variation is defined by a polynomial of the specified degree (constant, linear, or quadratic for the choices 0, 1, or 2, respectively).

Adverse responses can be defined in one of two ways. Either a background rate of adverse response is specified (e.g., a 5% rate of adverse response in the absence of exposure) or cut-off value(s) can be specified, with the assumption that values above or below (depending on the adverse direction) the cut-off(s) are adverse. The background rate of response need only be defined of the definition is in terms of background rate (probability) of response; the cut-off(s) need only be defined if the definition is in terms of cut point(s).

“Other Assignments” also allows the user to specify the number of bootstrap iterations to run to estimate confidence bounds. As shown in the example screen above, those bounds can be one-sided or (if the “Use Two Sided CI?” box is checked) two-sided.

The number of bootstrap iterations should be large enough to provide a stable estimate of the bounds. The Bootstrap Iteration value shown above (100) is almost certainly too low for a final, stable estimate of those bounds. Values on the order of 100 or more will probably be required in most cases; the user should perhaps do several runs to determine that the bound estimates have stabilized for the number of iterations chosen. Increasing the number of iterations will noticeably increase the time it takes to run the model.

Note For "Confidence Level" the user must actually enter a p value such that the level of confidence is (1-p)*100%. For example, in the example screen above, the "Confidence Level" field has the value 0.05. This corresponds to requesting 95% confidence limits: (1—0.05)*100% = 95%.

Study Description

Here, the user can supply any additional experiment-specific information that s/he wished to have reported in the output files.

Running the model

Once all the options have been specified as desired, clicking the **Run** button will initiate the repeated measures analysis. The run will produce a set of five graphs that will flash momentarily on the screen. When the run is complete, the full set of five plots will be available in a summary plot screen. The individual plots can be copied and pasted into other files (such as a Word document file).

See also:

- Repeated Response Measures Model Options Fields
- Repeated Response Measures Model Text Output
- Repeated Response Measures Model Description

CONCENTRATION X TIME DATA

The Concentration x Time Data model allows for fitting of dichotomous response data sets having two or more explanatory variables (as in acute inhalation toxicity experiments). The explanatory variables can be entered as main effects or in interaction (cross-product) terms. The user can request the value (and its bounds) of one explanatory variable when a response rate is specified (fixing the other explanatory variables at some user-specified values) and/or conversely, the value (and its bounds) of the response rate, given specification of all explanatory variables.

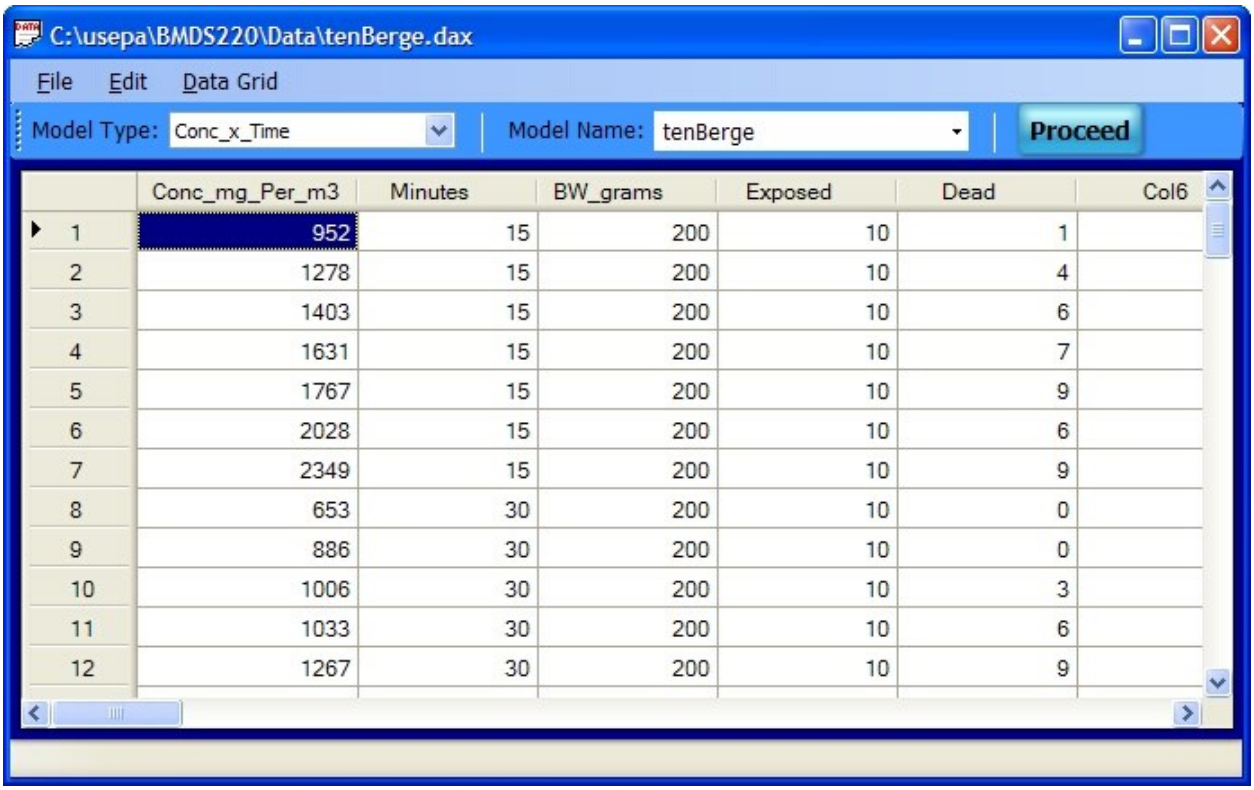
To start an analysis of Concentration x Time (CxT) data, open a new Data Grid window and enter or import the data, as you would for any other new dataset.

Once a dataset has been created and saved with a name that is not "Untitled," you can initiate an analysis of the data by selecting the Model Type as "Conc_x_Time" and clicking the **Proceed** button.

Note that currently there is only one model of this type (the so-called ten Berge model), which is selected by default. Of course, a previously saved dataset can

be opened as usual (from the **File** menu or using the **Open Dataset** toolbar button) and the Conc x Time model type selected, as described above.

The following screenshot shows the tenBerge.dax dataset included with BMDS.

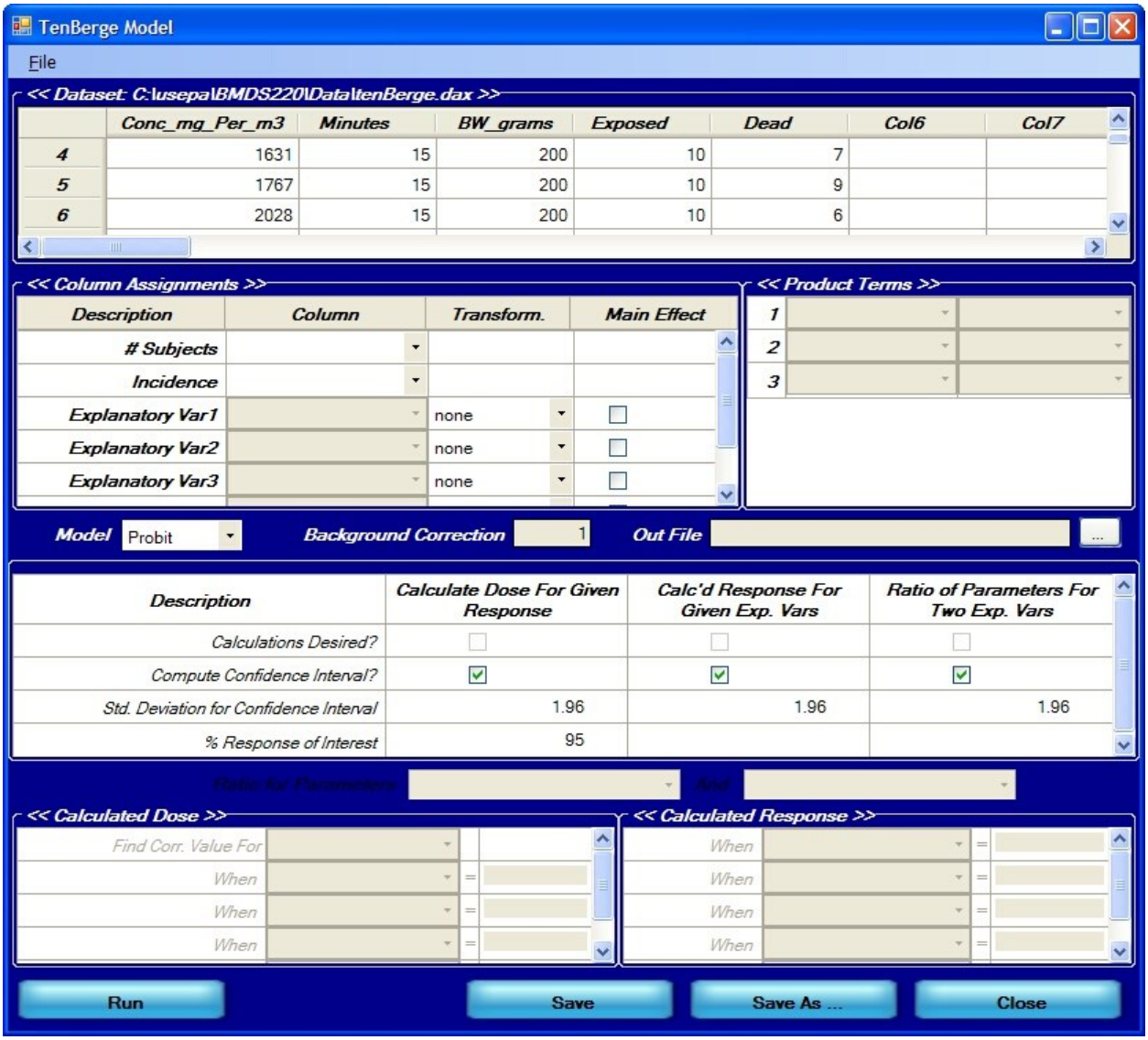


	Conc_mg_Per_m3	Minutes	BW_grams	Exposed	Dead	Col6
1	952	15	200	10	1	
2	1278	15	200	10	4	
3	1403	15	200	10	6	
4	1631	15	200	10	7	
5	1767	15	200	10	9	
6	2028	15	200	10	6	
7	2349	15	200	10	9	
8	653	30	200	10	0	
9	886	30	200	10	0	
10	1006	30	200	10	3	
11	1033	30	200	10	6	
12	1267	30	200	10	9	

For accurate results, please ensure the ten Berge dataset's structure conforms to the following sequence.

- The first columns in the dataset should be the Main Effect columns (e.g., Dose and Time). These columns can be in any order but they must appear first.
- The final columns in the dataset should be the # Subjects and Incidence columns, in that order.
- Other columns (e.g., Age, Litter) can appear in any order following the Main Effect columns but before the # Subjects and Incidence.

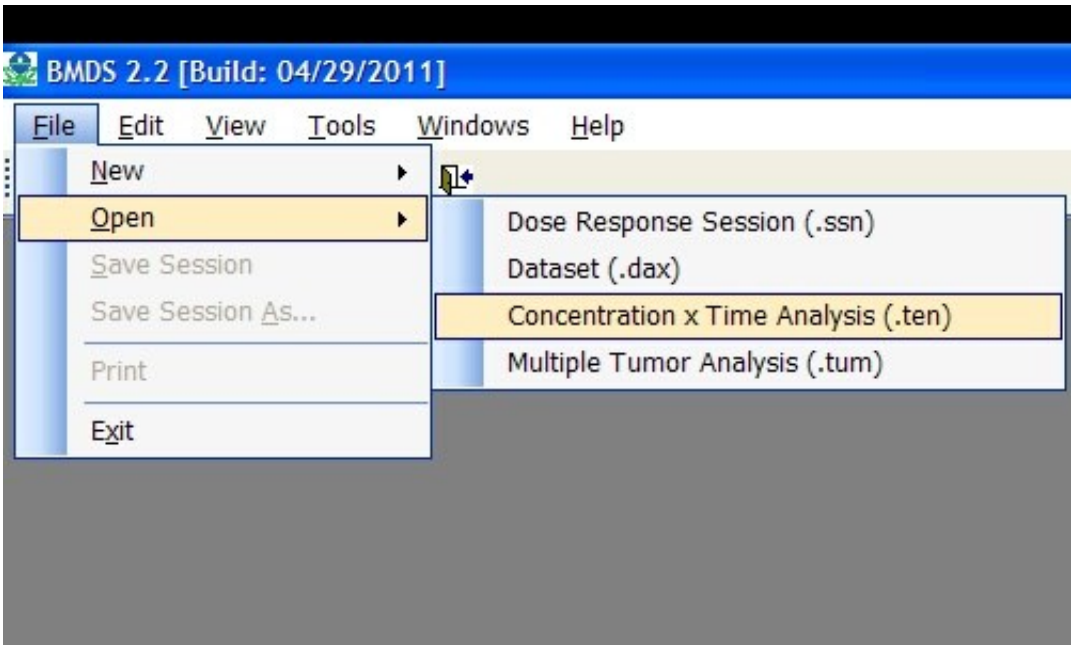
Selecting the **Proceed** button will open a special Model Option Screen specifically designed to facilitate modeling data with the Concentration x Time model.



Details on the specification of the option screen choices and running the model are provided in the section on Concentration x Time Option Screen.

The screenshot above shows that the Concentration x Time analysis that will be specified using the option screen can be saved (**Save** or **Save As** buttons).

A Concentration x Time analysis is saved with a ".ten" extension on the name of the user's choice. That extension should be used with all Concentration x Time analyses, so that they can be located and recalled for later use. Saved Concentration x Time analyses can be accessed through the **File** menu:



Currently, this is the only access to saved Concentration x Time analyses.

See also:

- Concentration x Time Option Screen
- Concentration x Time Model Description

MULTIPLE TUMOR ANALYSIS

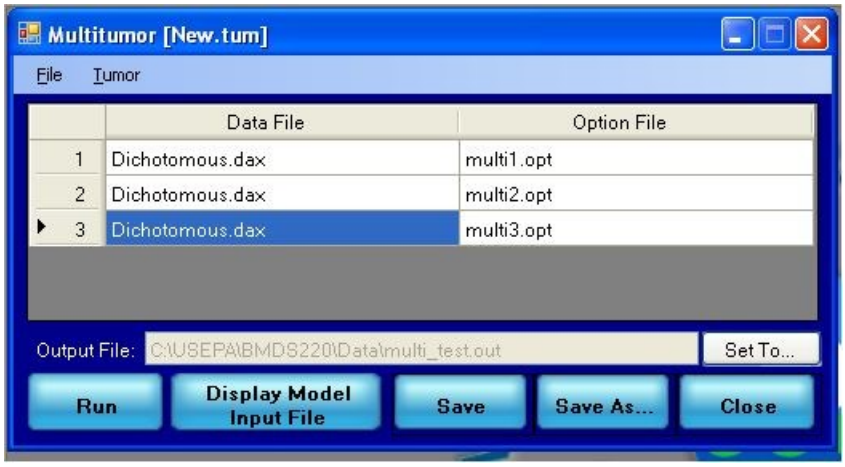
ASSUMPTIONS AND RESULTS

The analyses of multiple tumors have the following assumptions and results.

- The tumors are independent of one another.
- A multistage model is an appropriate model for each of the tumors separately. (The individual multistage-cancer models fit to the individual tumors need not have the same degree, however.)
- The user is interested in estimating the risk of getting one or more of the tumors being analyzed; the results indicate the BMD and BMDL associated with the user-defined benchmark response (BMR) level, where the BMD and BMDL are the maximum likelihood and lower bound estimates of the dose that is estimated to give an extra risk equal to the BMR for the “combination” (getting one or more of the tumors).

THE MULTIPLE TUMOR ANALYSIS SESSION SCREEN

A multiple tumor analysis uses a session screen somewhat similar to that used to facilitate the analysis of a dataset using multiple models. An example of a multiple tumor analysis session screen is shown here:



Note that in this case, there is no selection for Model Type (it is Dichotomous because the endpoints that are analyzed in these types of analyses are dichotomous, as in counts of animals with certain types of tumors). And there is no selection for Model Name; a Multiple Tumor Analysis will always run the Multistage-Cancer model (at present, only the Multistage-Cancer model is set up to analyze more than one dichotomous endpoint and combine the model fits to obtain a combined BMD and BMDL as described above).

The Data File and the Option File selections are exactly the same as when running a regular dose-response session in BMDS. Note that the Option Screen will be the one associated with a Multistage-Cancer Model. The user should ensure that the degree of the polynomial and other selections for modeling parameters are as desired for the particular dataset(s) being analyzed.

For example, if the user has previously analyzed a tumor using a 2nd degree model and found that to be the best choice for the tumor in question, s/he may want to set the degree of the polynomial for the analysis of the combination to the same degree—this can be ensured by using the same option file that was used, and saved, when the individual tumor was analyzed. In particular, the user should make sure that the risk levels (BMRs) selected in all the option files used in a multiple tumor analysis are the same and are at the level desired by the user.

Rows can be added or deleted from the Multiple Tumor Analysis screen by selecting the corresponding choice from the screen's Tumor menu.

Note There should be ***no empty or blank rows*** in the screen when the user clicks **Run** (e.g., no trailing empty rows at the bottom of the grid). Empty rows will cause the program to erroneously assume there is an additional tumor to be included in the analysis and result in an error. Empty rows can be eliminated by clicking on any cell in the row and then selecting **Tumor>Delete** from the screen's menu bar.

OBTAINING THE COMBINED BMD

Because of the form of the multistage-cancer model, the combined BMD is obtained in a relatively straightforward manner from the maximum likelihood parameter estimates from the models fit to the individual tumors. The combined maximum log-likelihood is the sum of the individual maximized likelihoods (summed over the individual tumor analyses). The combined BMD is the dose that is estimated to yield an extra risk of getting one or more of the tumors, where the extra risk is equal to the BMR. The calculation of the combined BMDL is a more complicated computation based on the profile-likelihood approach. As such, it gives the lowest value of the dose that satisfies the following conditions: there is a combination of parameters (across all models) for which the value of the BMDL gives a combined extra risk equal to the BMR and, using those parameter values, the combined log-likelihood is greater than or equal to a minimum log-likelihood defined by the maximum log-likelihood and the confidence level specified by the user (i.e., the parameters that give the desired extra risk when the dose is equal to the BMDL give a combined log-likelihood that is “close enough” to the maximum combined log-likelihood).

SAVING SESSIONS

Multiple Tumor Analysis sessions can be saved and opened at a later time (click the **Save** or **Save As** buttons at the bottom of the screen).

RUNNING AN ANALYSIS AND VIEWING RESULTS

Clicking the **Run** button will initiate the analysis and result in the creation of a single output file, the name and location of which can be set by the user by clicking **Set To …**

That output file will include analysis results for each individual tumor considered by itself plus, at the end of the output, a short section that shows the estimated BMD and BMDL for the BMR and confidence levels specified by the user. No graphical output is produced; the plots for the individual multistage model runs can be obtained by running the individual tumors in a usual data analysis or from within a regular dose-response session. It is basically presumed here that the user has already run analyses of the individual tumors to identify the endpoints of

interest (and to determine the best form of the multistage-cancer model for those selected tumors) that then will be used for the combined analysis. Hence, no additional graphics are produced.

TROUBLESHOOTING A TUMOR ANALYSIS

If one or more of the tumors is estimated to have a BMD greater than three times the highest dose tested (for that tumor), then the multiple tumor analysis will stop at an intermediate point, i.e., after the fitting has been done for the tumor in question and the magnitude of that BMD has been determined. No tumors listed below that tumor will be analyzed and no combination will be completed.

It is probably the case that the tumor in question will not add substantially to the estimation of a BMD for the combinations of tumors, assuming other tumors have BMDs less than three times the highest dose; that is because the magnitude of response for the tumor in question has not even reached the benchmark response level for such a high exposure and so its individual contribution to the risk of getting one or more of the tumors being analyzed will be small in comparison to that for the other tumors. The user might attempt a combination that does not include the tumor in question.

The input file (.d file) for a multiple tumor analysis need not be edited by the user; the BMDS GUI automatically creates such a file to reflect the user specifications in the Analysis Session screen (see above). If such a file is examined, the user will see that it consists of a concatenation of t Multistage Dichotomous .d files (starting with the line that specifies the number of dose groups and the desired degree of the model), all specifying that the beta parameters are restricted to be greater than or equal to zero), where t is the number of tumors being combined. Preceding that concatenation will be three lines of text (which have no bearing on the model selections) and then a line that specifies the value of t.

See also:

- Multistage Model
- Multistage Dichotomous Model Input File Format

DATA WITH NEGATIVE MEANS

Data with negative means should only be modeled with a constant variance model.

It may occasionally be the case that, when modeling transformed data, you will need to model negative data. In this case, the transformation used should be a

variance-stabilizing transformation so that a constant-variance model would be appropriate.

If a standard deviation-based BMR is used to define the BMD calculations, then a constant can be added to all the observations (or means) to make the values (means) positive. That will not change the standard deviations of the observations and would allow you to model the variance.

TEST FOR COMBINING TWO DATA SETS FOR THE SAME ENDPOINT

At this time, BMDS does not include a formal test for similarity of dose response across covariate values (e.g., across class variables like sex).

However, the following procedure can be used if you have dose-response data for two experiments that you are considering combining (e.g., for the two sexes within a species, or two species, etc.).

Test for combining two data sets for the same endpoint

1. Choose a single model to consider for both runs.
2. Model the two runs separately. For each run, record the following:
   - Maximum log-likelihood for each run. Add the numbers from each run to get the ***summed*** log-likelihood.
   - The number of unconstrained parameters for each run. Add the numbers from each run to get the ***summed*** unconstrained parameters.
3. Combine the data from the two experiments and model them together. Record the following:
   - The maximum log-likelihood for the combined run. This will be the ***combined*** log-likelihood.
   - The number of unconstrained parameters for the combined run. This will be the ***combined*** unconstrained parameters.
4. Subtract the combined log-likelihood from from the summed log-likelihood. Then, multiply the difference by 2.
5. Compare the value from Step 4 to a chi-squared distribution. The degrees of freedom for that chi-squared distribution will be the difference between the summed unconstrained parameters (Step 2) and the combined unconstrained parameters (Step 3).

   If the value from Step 4 is in the tail (say, greater than the 95th percentile) of the chi-squared distribution in question, then reject the null hypothesis

that the two sets have the same dose-response relationship. If rejection occurs, then infer that it is not proper to combine the two data sets.

OUTPUT FROM MODELS

TEXT OUTPUT FROM MODELS

The purpose of the BMDS output pages is to provide the user with goodness-of-fit criteria and model results to aid in determining the appropriateness of the subject model to the benchmark dose derivation. While BMDS will estimate parameters etc. for the user, it is the user's responsibility to interpret these results before making use of the BMDL.

The BMDS model text output also provides information relevant to whether or not the function maximization problem was actually accomplished. That is, for each model, parameters are estimated using Maximum Likelihood procedures through an iterative routine. There is no guarantee that the model parameters will in fact achieve the true maximization, and by inspecting the output pages, the user should be able to obtain at least some idea as to whether or not it was achieved. While all models tend to follow a similar format, there are some differences in the output pages given by certain models.

The output pages also give the user a quick verification of the options they had selected on the model option screen. For instance, when two users may be comparing results and obtained different answers, they may consult the output pages to make sure the settings were the same or if they had used the same (or most current) version of the software/models.

See also:

- Dichotomous Model Text Output
- Continuous Model Text Output
- Nested Model Text Output
- Graphics Output from Models

CONTINUOUS MODEL TEXT OUTPUT

The continuous output file starts with a few explanatory lines that the user can reference quickly to check/verify the version number, the date and time of run, the input dataset used, that all the correct options were set, which model was used, the explicit form of the dose response function for the model run, and review basic data summaries (number of dose levels, etc).

The output file is designed so that it will provide a reliable basis for reentering a BMDS dataset and accurately reproducing the results of a run (e.g., with an updated model) at a later date. The “form of the response function” is provided in

each model's text output file, and is the model function for which BMDS will estimate parameters in order to derive the Benchmark Dose.

Default Initial Parameters:

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate alternative initial parameter values should they want to rerun the program if a maximum wasn't found, not believable, etc.

Parameter Estimates:

The parameter estimates are the actual estimates the program has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons:

1. If standard errors are extraordinarily high, then the user may suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision.
2. To make inferences about the population parameters themselves. Under certain assumptions, the user may be able to formulate tests for the true value of the parameter.

Asymptotic Correlation Matrix of Parameter Estimates

This table provides the user with a matrix of correlation estimates between each of the parameters. Again, if these values seem to be high (in this case, very close to 1, in absolute value), there may have been a problem in the maximization. However, as stated before, high correlation does not confirm that the process of maximization did, in fact, fail.

Note The parameter standard errors and the correlation matrix elements are based on a variance-covariance (VCV) matrix obtained by inverting the negative of the Hessian matrix (the Fisher-observed information matrix). That matrix is made up of second partial derivatives of the log-likelihood, with respect to the model parameters. For all the continuous models, the partials are derived using a finite difference approximation to those derivatives.

Table of Data and Estimated Values of Interest

This table gives a listing of the data as well as estimated means and standard deviations from the model. This is a good place for the user to look, along with the Tests of Fit and Maximum Likelihood below, to judge the appropriateness of the model. If a model fits well, the observed and estimated

means should be relatively close. The scaled residual values printed in the final column of the table are defined as follows:

(Obs. Mean—Predicted Mean)/SE,

where the Predicted Mean is from the model and SE equals the estimated standard deviation (square root of the estimated variance) divided by the square root of the sample size.

The overall model should be called into question if the scaled residual value for any individual dose group, particularly a dose group close to the BMD estimate, is greater than 2 or less than -2.

See also:

- Text Output from Models—Introduction
- Continuous Models Option Screens
- Continuous Models—Description
- Graphics Output from Models
- Continuous Model Maximum Likelihood
- Tests of Fit

Continuous Model Maximum Likelihood

The BMDS uses likelihood theory to estimate function parameters and ultimately to make inferences based on risk assessment data. Maximum likelihood is the process of estimating the model parameters; the likelihood function is as large as possible (maximized) given the form of the model under consideration and the data. In other words, parameter values are “chosen” such that the subject model (e.g., polynomial or power) obtains the best possible fit to the data, given the constraints of the model's parameter structure. For example, suppose one wishes to fit a second degree polynomial model with a constant variance to a dataset. The particular form of this model would be:

Y = b0 + b1 * X + b2 * X^2

The parameters we wish to estimate in this case would be b0, b1, and b2, as well as the constant variance parameter, call it Sigma^2. To estimate these parameters, BMDS uses maximum likelihood procedures, the end result being a vector of parameters that maximizes the likelihood function for the model specified. The “Log(likelihood)” value given on the BMDS output page is the maximum value of the natural logarithm of the likelihood function. Also note that there are an associated number of parameters for each likelihood calculated. The number of parameters reported for the model under consideration is the total number possible for the model minus any parameter estimates that have values

on the bounds set for their estimation (either bounds specified by the user or those inherent to the model). In the example above, if all 4 parameters were estimated, and did not equal a bound (e.g., did not equal 0 for the b parameters), the number of parameters reported for the fitted model likelihood is 4.

The Akaike's Information Criterion (AIC) (Akaike, 1973; Linhart and Zucchini, 1986; Stone, 1998) value given on the BMDS output page is -2L + 2p, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model parameters estimated (and not on a boundary; see above). It can be used to compare different types of models which use a similar fitting method, as do all dichotomous, continuous and nested model types within BMDS. The model with the lowest AIC would be presumed to be the better model under this method. Although such methods are not exact, they can provide useful guidance in model selection.

The BMDS output file gives five likelihood and AIC values that may be of interest to the user. These values are later used in asymptotic Chi-Square tests of fit. Each of these likelihood values represents a model a user may consider in the analysis of the data. The five models are described in Table 26.

Table 26: *Models Automatically Fit by BMDS*

Model	Description
A1: “Full” Constant Variance Model	Y(i,j) = Mu(i) + e(i,j), Var{e(ij)} = Sigma^2
A2: “Fullest” Model	Y(i,j) = Mu(i) + e(i,j), Var{e(ij)} = Sigma(i)^2
A3: “Full” Model with variance structure specified by the user	Y(i,j) = Mu(i) + e(i,j), Var{e(ij)} = alpha*(Mu(i))^rho
R: “Reduced” Model	Y(i,j) = Mu + e(i,j), Var{e(i)} = Sigma^2
Fitted Model	The user-specified model

Model A1 estimates separate and independent means for the observed dose groups (it is “full” or “saturated” in that respect) but posits a constant variance over those groups.

Model A2 is the “fullest” model in that it estimates separate and independent means for the observed dose groups (as in Model A1) and it also estimates separate and independent variances for those groups. There is no assumed functional relationship among the means or among the variances across dose groups. This model is often referred to as the “saturated” model (it has as many mean and variance parameters as there are dose groups). The log-likelihood obtained for this model is the maximum attainable, for the data under consideration.

Model A3 is similar to model A2, and may only differ with respect to its variance parameters. Model A2 estimates separate and independent means for the observed dose groups (like A1). If the user specifies a constant variance for the fitted model, then model A3 will also assume that and it becomes identical to Model A1. If the user assumes a non-constant variance for the fitted model, then Model A3 will also assume the same functional form for the variance.

The reduced model (R) is the model that implies no difference in mean or variance over the dose levels. In other words, it posits a constant mean response level with the same variance around that mean at every dose level.

The last model, the fitted model, is the user-specified model (e.g., power or polynomial, among others). A user may have reason to believe that a certain model may describe the data well, and thus uses it to calculate the BMD and BMDL.

See Tests of Fit for a description of how these models are used to test certain hypotheses about the data.

See also:

- Text Output from Models
- Dichotomous Model Text Output
- Continuous Model Text Output
- Nested Model Text Output
- Graphics Output from Models
- Tests of Fit

Tests of Fit

The BMDS software provides four different Tests of Fit that the user may use to determine an appropriate model for fitting their data. These Tests of Fit are based on asymptotic theories of the likelihood ratio. Without getting too technical, the likelihood ratio is just the ratio of two likelihood values, many of which are given in the BMDS output. Statistical theory proves that -2*log(likelihood ratio) converges to a Chi-Square random variable as the sample size gets large and the number of dose levels gets large. These values can in turn be used to obtain approximate probabilities to make inferences about model fit. Chi-Square tables can be found in almost any statistical book.

Each of the five models, described in the section on likelihood, has a likelihood value. The BMDS program uses these values to create ratios from two models that form a meaningful test. Suppose the user wishes to test two models, A and B, for fit. One assumption that is made for these tests is that model A is “nested within” Model B, i.e., that Model B can be simplified (via restriction of some

parameters in Model B) in such a way that the simplified model is Model A. This implies that Model A has fewer varying parameters. As an example, consider that the linear model is a "simpler" or "nested" model relative to the power model because the linear model has the power parameter restricted to be equal to 1.

Note The model with a higher number of parameters is always in the denominator of this ratio.

Now, using the theory, -2*log{ L(A)/L(B)} approaches a Chi-Square random variable. This can be simplified by using the fact that the log of a ratio is equal to the difference of the logs, or simply put,

-2*log{ L(A)/L(B)} = -2*(log{L(A)} - log{L(B)}) = 2*log{L(B)} - 2*log{L(A)}.

The likelihood values given by BMDS are in fact the log-likelihoods, log{L(B)} and log{L(A)}, so this likelihood ratio calculation becomes just a subtraction problem. This value can then in turn be compared to a Chi-Square random variable with a specified number of degrees of freedom.

As mentioned in the section on likelihood, each log likelihood value has an associated number of parameters. The number of degrees of freedom for the Chi-Square test statistic is merely the difference between the two model parameter counts. In the mini-example above, suppose Model A has 5 fitted parameters, and that Model B has 8. In this case, the Chi-Square value you would compare this to would be a Chi-Square with 8-5 = 3 degrees of freedom.

In the A vs B example, what is exactly being tested? In terms of hypotheses, it would be:

H0: A models the data as well as B

H1: B models the data better than A

Keeping these tests in mind, suppose 2*log{L(B)} - 2*log{L(A)} = 4.89 based on 3 degrees of freedom. Also, suppose the rejection criteria is a Chi-Square probability of less than .05. Looking on a Chi-Square table, 4.89 has a p-value somewhere between .10 and .25. In this case, H0 would not be rejected, and it would seem to be appropriate to model the data using Model A. BMDS automatically does the "table look-up" for the user, and provides the p-value associated with the calculated log-likelihood ratio having degrees of freedom as described above.

The BMDS software provides four default tests. BMDS provides interpretation of the test results, based on p-values that have been selected by EPA. However, the computed p-values are presented so that the user is free to use any rejection criteria they want. Each of the four default tests provided for any of the continuous models is discussed in some detail below.

Test 1 (A2 vs R): Tests the null hypothesis that responses and variances don't differ among dose levels. If this test fails to reject the null hypothesis, there may not be a dose-response.

This test compares Model R (the simpler model) to Model A2. Model R is a simpler A2 (or nested within A2) since R can be obtained from A2 by restricting all the mean parameters to be equal to one another and restricting all the variance parameters to be equal to one another. If this test fails to reject the null hypothesis, then there may not be a dose-response, as the inference would be that the simpler model (R) is not much worse than the saturated model. The default p-value for the test (as reported in the Tests of Interest section of the output) is 0.05. A p-value less than 0.05 is associated with the statement that "There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data." A p-value greater than 0.05 is associated with the statement that the data may not be suitable for dose-response modeling.

Test 2 (A1 vs A2): Tests the null hypothesis that variances are homogeneous. If this test fails to reject the null hypothesis, the simpler constant variance model may be appropriate.

This test compares A1 (the simpler model) to Model A2. Model A1 is a simpler A2 (or nested within A2) since A1 can be obtained from A2 by restricting all the variance parameters to be equal to one another. If this test rejects the null hypothesis, the inference is that the constant variance assumption is incorrect and a modeled variance is necessary to adequately represent the data. The default p-value for the test (as reported in the Tests of Interest section of the output) is 0.1. A p-value less than 0.1 is associated with the statement that the user should "Consider running a non-homogeneous variance model. A p-value greater than 0.1 is associated with the statement that a constant variance assumption is suitable for the dose-response modeling.

Test 3 (A3 vs A2): Tests the null hypothesis that the variances are adequately modeled. If this test fails to reject the null hypothesis, it may be inferred that the variances have been modeled appropriately.

Here, the test is one to see whether or not the user-specified variance model, is appropriate. If the user-specified variance model is "constant variance," then Models A1 and A3 are identical; this test is the same as Test 2, with the same interpretation. If the user-specified variance model is nonconstant (Sigma(i)^2 = alpha*Mu(i)^rho), this test determines if that particular equation appears adequate to describe the variance across dose groups. Model A3 is the simpler version of Model A2 obtained by constraining the variances to fit the nonconstant variance equation. The default p-value for the test (as reported in the Tests of Interest section of the output) is 0.1. A p-value less than 0.1 is associated with the statement that "You may want to consider a different variance model." [Unfortunately BMDS has no further way to model

variance. Look for different variance models in future releases of BMDS.] A p-value greater than 0.1 is associated with the statement that the modeled variance appears to be suitable for the dose-response modeling.

Test 4 (Fitted vs A3): Tests the null hypothesis that the model for the mean fits the data. If this tests fails to reject the null hypothesis, the user has support for the selected model.

This test compares the Fitted Model to Model A3. The Fitted Model is as simpler Model A3 (or nested within Model A3) because it can be obtained by restricting the means (unrestricted in A3) to be described by the dose-response function under consideration. If this test fails to reject the null hypothesis, the inference is that the fitted model is adequate to describe the dose-related changes in the means (conditional on the form of the variance model; the form of the variance model is the same for the Fitted Model and Model A3). Failure to reject the null hypothesis is associated with the inference that the restriction of the means to the shape of the dose-response function under consideration is adequate. The default p-value for the test (as reported in the Tests of Interest section of the output) is 0.1. A p-value less than 0.1 is associated with the statement that "You may want to try a different model." I.e., the fit of the Fitted Model is not good enough. A p-value greater than 0.1 is associated with a statement that the Fitted Model appears to be suitable for dose-response modeling.

See also:

- Text Output from Models
- Dichotomous Model Text Output
- Continuous Model Text Output
- Nested Model Text Output
- Graphics Output from Models
- Continuous Model Maximum Likelihood Help

DICHOTOMOUS MODEL TEXT OUTPUT

The dichotomous output page starts with a few explanatory lines that the user can reference quickly to: check the version number, the date and time of run, the input dataset used, check which model was used, see the explicit form of the response function, verify that all the correct options were set and get some basic data summaries (number of dose levels, etc). The output page is designed so that it will provide a reliable basis for reentering BMDS and accurately reproducing the results of a run (e.g., with an updated model) at a later date. The "form of the response function" is provided on each model's text output page, and

is the model function that BMDS will estimate parameters for in order to derive the Benchmark Dose.

Default Initial Parameters

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate parameter values should they want to rerun the program if a maximum wasn't found, they just don't believe the answer, etc.

Parameter Estimates

The parameter estimates are the actual estimates the program routine has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons:

1. If standard errors are extraordinarily high, then the user should suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision.
2. To make inferences about the population parameters themselves. Under certain assumptions, the user may be able to formulate tests for the true value of the parameter.

Asymptotic Correlation Matrix of Parameter Estimates

This table provides the user with a matrix of correlation estimates between each of the parameters. Again, if these values seem to be high (in this case, very close to 1), there may have been a problem in the maximization. Also, as stated before, high correlation does not confirm that the problem of maximization in fact failed. The Weibull model, for instance, tends to give high correlation between the slope and power parameters, even when the likelihood was maximized.

Note The parameter standard errors and the correlation matrix elements are based on a variance-covariance (VCV) matrix obtained by inverting the negative of the Hessian matrix (the Fisher-observed information matrix). That matrix is made up of second partial derivatives of the log-likelihood, with respect to the model parameters.

For all the dichotomous models, except for the multistage and multistage cancer models, the partials are derived using a finite difference approximation to those derivatives.

For the multistage and multistage cancer models, the partial derivatives are computed analytically (i.e., without approximating their values through the finite-difference method).

Analysis of Deviance Table

The analysis of deviance table lists three maximum likelihood values. The first is the “full model”. The full model would be any model that would perfectly fit all the positive response proportions at the dose levels specified by the user. The second model is the “fitted model” maximum likelihood value. This is the value of the maximum likelihood function for the particular model selected and using the estimated parameter values. The last likelihood value is the “reduced model” value, which would be the value of the likelihood function if all data points where assumed to come from the same population with the same population parameter. That is, for each dose level, the actual probability of an adverse effect would be the same. These values are just the likelihood functions evaluated according to the assumptions made at each step (i.e., the model assumption for the fitted model).

Next to the likelihood values there are three values: Deviance, degrees of freedom (DF), and P-value. The Deviance is the difference between the fitted or reduced model and the full model likelihood values. This deviance measures whether or not the smaller model (i.e., the fitted or reduced model) describe the data as well as the full model does. This deviance is then used to formulate a Chi-Square random variable that tests exactly that. The user may choose a rejection level (.05 is common) to test whether or not the model fit is appropriate. The p-value for testing whether or not the fitted model adequately describes the data is given next to the fitted model likelihood, and the user can reject or not reject a hypothesis according to the p-value given . The reduced model p-value would be used in the same way, but here the user would be testing whether or not there is in fact a dose/response relationship where the true population proportion is a function of dose, as opposed to a single population with one parameter (the proportion of affected animals).

It will often happen that several models provide an adequate fit to a given dataset. These models may be essentially unrelated to each other (for example a logistic model and a probit model often do about as well at fitting dichotomous data) or they may be related to each other in the sense that they are members of the same family that differ in which parameters are fixed at some default value. One can consider the log-logistic, the log-logistic with non-zero background, and the log-logistic with threshold and non-zero background to all be members of the same family of models. Generally, within a family of models, as additional parameters are introduced the fit will appear to improve. Goodness-of fit statistics presented in the main body of the Analysis of Deviance Table can be used to compare such related models, but are not designed to compare unrelated models. Alternative approaches are need for selecting between models that are not related (not in the same family).

The Akaike's Information Criterion (AIC; Akaike, 1973; Linhart and Zucchini, 1986; Stone, 1998) is defined as -2L + 2p, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model parameters estimated. The AICs for the model run are provided at the bottom of the Analysis of Deviance Table. They can be used to compare different types of models which use a similar fitting method (for example, least squares or a binomial maximum likelihood), as do all dichotomous, continuous and nested model types within BMDS. The model with the lowest AIC would be presumed to be the better model under this method. Although such methods are not exact, they can provide useful guidance in model selection.

Goodness of Fit

This table gives both a listing of the data as well as residual and overall Chi-Square Goodness of Fit tests. This is a good place for the user to look outside of the Analysis of Deviance table to judge the appropriateness of the model. The table lists estimated probabilities, the expected and observed number of affected animals and scaled residuals for each dose group. If a model fits well, the observed and expected number of affected animals should be relatively close. The overall scaled residual value, and it corresponding p-value are indications of that “closeness”. If the p-value is larger than some predetermined critical p-value, then the user may be able to conclude that the model is appropriate to model the data.

The scaled residual values printed at the end of the table are defined as follows:

(Obs.—Expected)/SE

where “Expected” is the predicted number of responders from the model and SE equals the estimated standard error of that predicted number. For these models, the estimated standard error is equal to sqrt[n*p*(1-p)], where n is the sample size and p is the model-predicted probability of response.”

n is the sample (litter) size, and

p is the model-predicted probability of response.

The overall model should be called into question if the scaled residual value for any dose group, particularly a low dose group, is greater than 2 or less than -2.

Slope at ED(10)—Cancer Model Only

Some additional assessment tools are imparted by the Cancer model at this time. The output page for the cancer model includes an estimate of the slope of the BMD curve at the ED(10) (the 10 percent extra risk response level) and the two sided 95.0% confidence interval for the slope at the ED(10). The two

sided 95.0% confidence interval for the linear term of the model is also provided. Finally, scaled residuals are reported to aid in determining how well the model fits the data at low doses.

Benchmark Dose Computation

This is the ultimate goal of the BMDS software (see Overview). The BMD or BMDL is the value that the user will use when determining the RfD or RfC for the particular toxicant being studied. The user should investigate all the output to this point, and then make the decision to accept this as a valid BMDL.

See also:

- Text Output from Models—Introduction
- Dichotomous Model Option Screens
- Dichotomous Model Descriptions
- Graphics Output from Models

Nested Model Text Output

The nested model output page starts with a few explanatory lines that the user can reference quickly to: check the version number, the date and time of run, the input dataset used, verify that all the correct options were set, check which model was used, see the explicit form of the mean function for the model run, and get some basic data summaries (number of dose levels, etc). The output page is designed so that it will provide a reliable basis for reentering BMDS and accurately reproducing the results of a run (e.g., with an updated model) at a later date. The “form of the response function” is provided on each model's text output page, and is the model function that BMDS will estimate parameters for in order to derive the Benchmark Dose.

Default Initial Parameters

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate parameter values should they want to rerun the program if a maximum wasn’t found, they just don’t believe the answer, etc.

Parameter Estimates

The parameter estimates are the actual estimates the program routine has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons:

1. If standard errors are extraordinarily high, then the user should suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision.
2. To make inferences about the population parameters themselves. Under certain assumptions, the user may be able to formulate tests for the true value of the parameter.

Note The parameter standard errors are based on a variance-covariance (VCV) matrix obtained by inverting the negative of the Hessian matrix (the Fisher-observed information matrix). That matrix is made up of second partial derivatives of the log-likelihood, with respect to the model parameters. For all the nested models, the partials are derived using a finite difference approximation to those derivatives.

Analysis of Deviance Table

The analysis of deviance table lists three maximum likelihood values.

- The first is the “full model”. The full model would be any model that would perfectly fit all the positive response proportions at the dose levels specified by the user.
- The second model is the “fitted model” maximum likelihood value. This is the value of the maximum likelihood function for the particular model selected and using the estimated parameter values.
- The last likelihood value is the “reduced model” value, which would be the value of the likelihood function if all data points where assumed to come from the same population with the same population parameter. That is, for each dose level, the actual probability of an adverse effect would be the same.

These values are the likelihood functions evaluated according to the assumptions made at each step (i.e., the model assumption for the fitted model).

Next to the likelihood values there are three values: Deviance, degrees of freedom (DF), and P-value. These are asymptotic Chi-Square tests that investigate the appropriateness of the model fit, as well the reduced model.

- The Deviance is the difference between the fitted or reduced model and the full model likelihood values. This deviance measures whether or not the smaller model (i.e., the fitted or reduced model) describe the data as well as the full model does. This deviance is then used to formulate a Chi-Square random variable that tests exactly that. The user may choose a

rejection level (.05 is common) to test whether or not the model fit is appropriate.

- The p-value for testing whether or not the fitted model adequately describes the data is given next to the fitted model likelihood, and the user can reject or not reject a hypothesis according to the p-value given .
- The reduced model p-value would be used in the same way, but here the user would be testing whether or not there is in fact a dose/response relationship where the true population proportion is a function of dose, as opposed to a single population with one parameter (the proportion of affected animals).

Goodness of Fit Information—Litter Data and Grouped Data

Both of these tables provide a listing of the data, expected and observed responses and scaled residuals (observed—expected).

The “Litter Data” table contains this information for each litter.

To obtain the “Group Data” table, the Litter Data were sorted on Dose (first), and by Litter Specific Covariate within Dose. Within dose, litters adjacent to each other with respect to Litter Specific Covariate were grouped together until the expected number of affected pups was at least one. This grouping was done prior to the estimation of an overall Chi-Square and p-value to improve the validity of the Chi-Square approximation for the goodness of fit statistic. Goodness of Fit statistics. Both tables list estimated probabilities, the expected and observed number of affected animals and scaled residuals for each dose group. If a model fits well, the observed and expected number of affected animals should be relatively close. The overall Chi-Square value and its corresponding p-value are an indication of that “closeness”. If the p-value is larger than some predetermined critical p-value, then the user may be able to conclude that the model is appropriate to model the data.

The scaled residual values printed at the end of the table are defined as follows:

(Obs. - Expected)/SE

where “Expected” is the predicted number of responders from the model and SE equals the estimated standard error of that predicted number. For these models, the estimated standard error is equal to sqrt[n*p*(1-p)*(θ*(n-1)+1)], where

n is the sample (litter) size,

p is the model-predicted probability of response, and

θ is the model-predicted intra-litter correlation coefficient.

The overall model should be called into question if the scaled residual value for any individual dose and litter-specific covariate combination, particularly for a low dose group, is greater than 2 or less than -2.

Benchmark Dose Computation

This is the ultimate goal of the BMDS software (see Overview). The BMD or BMDL is the value that the user will use when determining the RfD or RfC for the particular toxicant being studied. The user should investigate all the output to this point, and then make the decision to accept this as a valid BMDL.

See also:

- Text Output from Models—Introduction
- Nested Models Option Screens
- Nested Models—Description
- Graphics Output from Models

REPEATED RESPONSE MEASURES MODEL TEXT OUTPUT

The Repeated Response Measures Model output file begins with a section that echoes user-specified information (e.g. Study Name and Study Description) as well as some information about the contents of the dataset: what the dose levels are, at what times observations were available, and the sample size (i.e., the number of distinct combinations of experimental unit ID and time). The user should verify that these values are correct; if they are not, then the data file should be checked for data entry errors.

In addition, this section shows the form of the model.

Likelihood-Related Estimates

The AIC and BIC as well as the log-likelihood for the model fit to the data being analyzed are shown here.

Random Effects

This section shows which parameters were selected to have random effects around the main (fixed) effect. At this time, the only parameter for which random effects are specified is the parameter A0 (the constant term in the background response polynomial). So, in this section there will be a standard deviation reflecting the variability of the random effects around the corresponding fixed effect. There will also be a “Residual” standard deviation reflecting the remaining variability that is not part of the random effect (reflecting the remaining lack of fit of the model to the data and therefore associated with residuals). The distributions of the random effects and of the

residuals are assumed to be independent of one another. [At a later time, when more than one random effect is allowed, the distributions of the random effects will not be assumed to be independent of one another, though they all will still be assumed independent of the residual distribution. In the case of more than one random effect, pair-wise correlation estimates will be provided as well. When those correlations are close to 1 or -1, that may be a strong indication that the data cannot support that many random effects and alternative assumptions should be tried by the user.]

Parameter Estimates

In this section, the additional results related to the model fitting are provided. Parameter estimates for the fixed effects are shown with their standard errors. In addition the degrees of freedom, t-test statistic value, and associated p-value for that test are shown, in order to facilitate evaluation of the significance of the parameters.

In addition, parameter correlations and a summary of the within-group residuals are shown.

Initial Values

In this section one finds the set of initial values that were used when the model apparently converged to an acceptable answer. Below that is the list of the initial values that the model was scheduled to try; it starts with the first set listed and continues until it uses a set that resulted in apparent convergence.

BMD Estimation

In this section the summary BMD results are presented. First, the user-specified choices for risk type, spontaneous risk level (adverse level; if a Cut Point was used instead of Background Rate, then the value of the cut point would be printed here), the area of adverse effects (Adverse Direction), and the BMR level are shown. If these are not the choices the user wants to have, the option file should be revisited and correct values entered for these fields. The same is true of the number of bootstrap iteration which is shown next.

The minimum BMD is what is shown (the BMD, as a rule, varies as a function of time). The time at which that minimum BMD was obtained is also given. The value shown for “Confidence Level” is (1-α)*100% (where α is what was entered on the option screen). The lower limit presented is based on the user-specified number of bootstrap iterations. As discussed elsewhere, the user should test for stability of that estimate if the accuracy of the BMDL (or BMDU if that too is estimated) needs to be assured to some desired number of significant digits.

In addition to the text output file, five plots are produced with each run.

See also:

Repeated Response Measures Option Screen

CONCENTRATION X TIME MODEL TEXT OUTPUT

The Concentration x Time model output file begins with a section giving information about the version number and build date of the program, as well as identifying the input dataset used to create the output and the name of the file that has the information needed to later produce graphics. [Currently, BMDS does not produce graphics for the Concentration x Time model.]

Model Specifications

This section provides the overview of the framework for the model, including the reference for Finney (1971) from which Wil ten Berge identified the probit analysis approach. The general form of the model as it is now implemented is presented here as is a basic summary of the number of input parameters (possible explanatory variables) and the number of observations in the dataset.

Input dataset Echo

This section should contain exactly the data that the user has included in the input file. If there are any errors here, the user should go back to the input file and correct the input values, and then rerun the analysis.

Modeling Choices

In this section, the following information is provided: the choices for the range of observations to analyze, the transformations of the input parameters to use, the link function (logit or probit), and the variable identifier numbers associated with the selected explanatory variables (single input parameters or products of pairs of input parameters). If any of this information does not correspond to the desired analysis, the user must go back to the input file to make corrections to the coding in the modeling section.

Fit and Parameter Estimates

The chi-square evaluation of fit and the degrees of freedom associated with the model fit to the selected data are given. The fit is assessed in relation to the “saturated” model having as many parameters as observations. The maximum likelihood estimates of the Bi coefficients are shown as is a Student t value that can be used to determine whether each of those terms is “statistically significant.” Variance and covariance estimates for each of the Bi terms are provided.

When the model fails, one or more of the parameter values may have a value of the form “-1.#J” or a similar non-number. This is an indication that the

model has not converged to an answer. The user should check the input file (also reflected in the data echo section of the output file) to see if some data entry errors are contributing to that problem.

If there are no errors in the input data, it is entirely possible that there is no solution for some data; this happens, for example, when there are only groups with either 0% or 100% response. In such cases, the model cannot determine a maximum likelihood and returns values for one or more of the parameters (and estimates depending on those parameters) that are of the form “-1.#IOe+000,” “1.#R,” “1.#QOe+000,” “1.#QNAN0,” or similar indications that no numerical answer was available. It is known, for example, that probit slope estimates can be infinite in some situations where concentrations with and without response are not suitably intermingled. A sufficient (but not necessary) condition to avoid this is to have two distinct doses with partial response.

“Dose” Estimation

In this section one finds the estimate of an input variable value that, for a given response and for specified values of the other input parameters, gives that response rate. Confidence limits are estimated if requested. Some reviewers have strongly suggested that the Student T-based deviates always be used and (confidence intervals obtained when a standard normal deviate is used are “too tight”) and so one might want to obtain from statistical tables the deviate for a T-distribution having degrees of freedom equal to the number of observations minus the number of estimated parameters (e.g., the 95th percentile from such a T-distribution). These same comments also apply to the next two sections giving estimates and confidence intervals for response rates and for the ratios of model parameters.

Notes The use of the terminology "probability of correct model" in the output file is not a good choice for describing the results of the chi-squared goodness-of-fit test that is the basis for the reported p-value. Subsequent versions of this software will replace that terminology with a statement like "The p-value associated with the chi-square goodness of fit test equals x" where x is the calculated p-value.

The terminology as shown in the example output file has been retained so that comparisons between the new version and the original version of the ten Berge software could be more easily made (the same description has been retained in both cases).

Similarly, the statement that the "prediction of the model is not sufficient" will be modified to simply indicate whether or not the p-value is greater than or less than 0.05, with the appropriate statement regarding adequate fit of the model or not (similar to the evaluations of fit in other BMDS models) and a suggestion that (if the model is not fitting the data well) the correction factor be applied to the variance and covariance estimates as well as selecting the deviate from the Student T distribution rather than the standard normal distribution.

Currently, neither the variance-covariance correction nor the choice of the deviate are done automatically for the calculation of confidence limits.

Response Estimation

Much like the previous section, this section provides estimates of the response associated with specified values of the input variables used in the model. When a deviate is given, the corresponding confidence interval is also calculated for that estimate. Note that the deviate supplied need not be the same as the one provided for the "dose" estimation, in case different confidence levels may be desired for dose and response estimates.

See notes in previous section about terminology related to the model fit.

Ratio Estimation

In this section the ratio of the Bi coefficients request by the user will be reported. As in the previous sections the confidence interval is also shown, if requested, at a level consistent with the specified deviate.

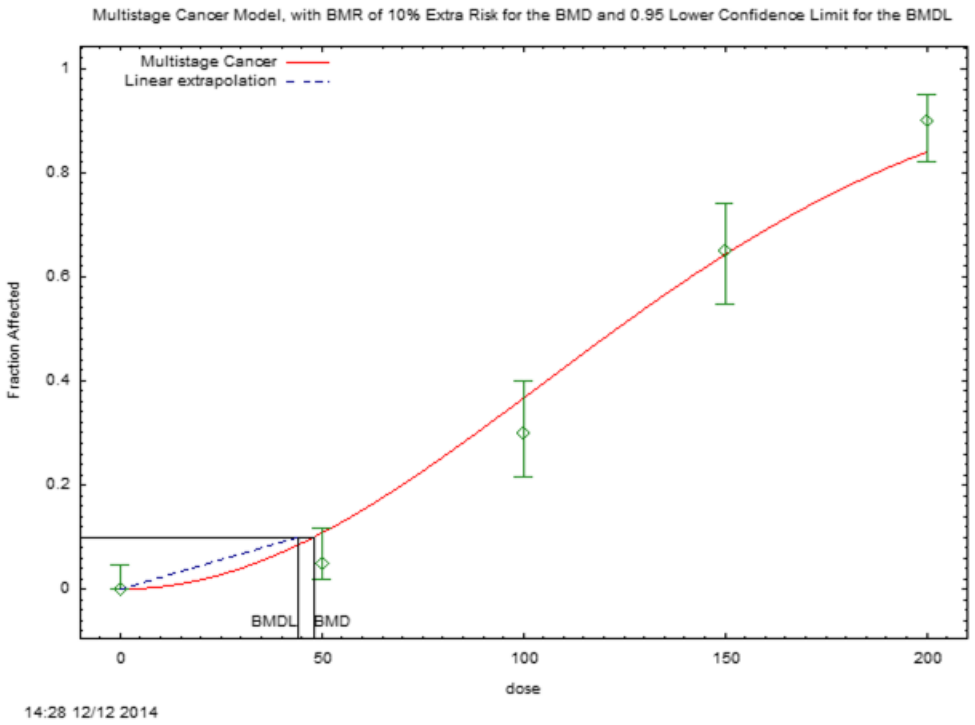
See notes in previous section about terminology related to the model fit.

See also:

- Concentration x Time Data
- Concentration x Time Model Option Screen

GRAPHIC OUTPUT FROM MODELS

The graphic output plot should display along with the text output file after each model run.



- The BMD and BMDL are identified on the plot as black vertical lines and are associated with the response level associated with the user-selected BMR, the horizontal black line.
- The BMD curve estimated by the model is represented by a red line and the BMDL curve (which is basically connecting five BMDL estimates) is represented by the blue line.
- Data points are shown in green with their individual group confidence intervals (see the section Error Bar Calculations for more information).

The graphic display features can be modified by either using GnuPlot edit features or copying the plot to your computer's clipboard and pasting it into another application capable of performing vector graphic editing (e.g., Microsoft PowerPoint). These copy and edit features are accessible by left-clicking on the small graphic icon at the top of the plot page or right-clicking on the graph. A menu will appear that enables you to modify the plot window in various ways.

Among the options available are:

- Copying to the clipboard
- Changing background

- Color and font specifications
- Printing options, including printing landscape or portrait.

ERROR BAR CALCULATIONS

Continuous Models

BMDS uses a single error bar plotting routine for all continuous models.

- The plotting routine calculates the standard error of the mean (SEM) for each group. The routine divides the group-specific observed variance (obs standard deviation squared) by the group-specific sample size.
- The routine then multiplies the SEM by the Student-T percentiles (2.5th percentile or 97.5th percentile for the lower and upper bound, respectively) appropriate for the group-specific sample size (i.e., having degrees of freedom one less than that sample size). The routine adds the products to the observed means to define the lower and upper ends of the error bar.

Dichotomous Models

The error bars shown on the plots of dichotomous data are derived using a method discussed in J. Fleiss, “Statistical Methods for Rates and Proportions” (Third Edition, 1973), pp. 26–29. That method is a modification of the Wilson interval (based on the score statistic) but with a continuity correction. For the upper bound, the calculation finds the proportion, pi, such that

(|p—pi|—1/(2n)) / sqrt(pi * (1—pi) / n) = z

where

p is the observed proportion

n is the total number in the group in question

z = Z(1-alpha/2) is the inverse standard normal cumulative distribution function evaluated at 1-alpha/2

This leads to equations for the lower and upper bounds of:

LL = {(2np + z2 - 1) - z * sqrt[z2 - (2 + 1/n) + 4p(nq + 1)]} / [2(n + z2)]

UL = {(2np + z2 + 1) + z * sqrt[z2 + (2 - 1/n) + 4p(nq -1)]} / [2(n + z2)]

where q = 1-p.

The error bars shown in BMDS plots use alpha = 0.05 and so represent the 95% confidence intervals on the observed proportions (independent of model).

Nested Models

The error bars shown for the plots of nested data are calculated in the same way as those for dichotomous data. However, a Rao-Scott transformation is applied prior to the calculations in order to express the observations in terms of an "effective" number of affected divided by the total number in each group (the format required for the confidence intervals of simple dichotomous responses).

MODEL DESCRIPTIONS

MODELS INCLUDED IN BMDS 2.6.0.1

The following list details the models, their filenames, and version numbers contained in this BMDS version.

DICHOTOMOUS MODELS

Filename	Version (Date)	Model(s) Included
Cancer.exe	3.4 (05/02/2014)	Multistage Cancer Model
Gamma.exe	2.16 (02/28/2013)	Gamma Model
Logist.exe	2.14 (02/28/2013)	Logistic and Log-Logistic Models
Multistage.exe	3.4 (05/02/2014)	Multistage Model
Probit.exe	3.3 (02/28/2013)	Probit and Log Probit Models
Weibull.exe	2.16 (02/28/2013)	Weibull and Quantal Linear Models

CONTINUOUS MODELS

Filename	Version (Date)	Model(s) Included
Exponential.exe	1.10 (01/12/2015)	Exponential Model
Hill.exe	2.17 (01/28/2013)	Hill Model
Poly.exe	2.20 (10/22/2014)	Polynomial and Linear Models
Power.exe	2.18 (05/19/2014)	Power Model

NESTED DICHOTOMOUS MODELS

Filename	Version (Date)	Model(s) Included
NCTR.exe	2.13 (04/27/2015)	NCTR Model
Nlogist.exe	2.20 (04/27/2015)	Nlogistic Model
Raivr.exe	2.12 (04/27/2015)	RaiVR Model

DICHOTOMOUS ALTERNATIVE MODELS

Filename	Version (Date)	Model(s) Included
Cancer_BG_Dose.exe	3.1 (12/10/2014)	Cancer Model with Background Dose
DichoHill.exe	1.3 (02/28/2013)	Dichotomous Hill Model
Gamma_BGDose.exe	1.4 (01/12/2015)	Gamma Model with Background Dose
Log_Probit_BG_Dose.exe	1.4 (01/12/2015)	Log Probit Model with Background Dose
Logist_BG_Response.exe	3.1 (01/12/2015)	Logistic Model with Background Response
Multistage_BG_Dose.exe	3.1 (12/10/2014)	Multistage Model with Background Dose
Probit_BG_Response.exe	2.9 (01/12/2015)	Probit Model with Background Response
Weibull_BG_Dose.exe	1.2 (01/12/2015)	Weibull Model with Background Dose

REPEATED RESPONSE MEASUREMENTS

Filename	Version (Date)	Model(s) Included
ToxicoDiffFunction.R, ToxicoDiffProgram.R	1.1 (09/23/2008)	Toxicodiffusion Model

CONCENTRATION X TIME

Filename	Version (Date)	Model(s) Included
TENBERGE.EXE	1.0 (12/26/2006)	ten Berge CxT Model

MULTIPLE TUMOR ANALYSIS

Filename	Version (Date)	Model(s) Included
MS_COMBO.EXE	1.8 (04/30/2014)	Multiple tumor analysis; combining multistage-cancer model runs over different tumors

OUTPUT FILE NAMING CONVENTIONS

BMDS automatically assigns an output file name for each model run (session row) corresponding to the following naming convention:

```
[3 letter model abbreviation]-[name of data file]-[name of option
file].out
```

For example, an output file named “web_Dichotomous_Opt.out” signifies this is output from the Weibull background dose model.

The following table presents the 3-letter model abbreviation for each BMDS model that generates an .out file.

CONTINUOUS MODELS

Model Type	Abbreviation
Exponential	exp
Hill	hil
Linear	lin
Polynomial	ply
Power	pow

DICHOTOMOUS MODELS

Model Type	Abbreviation
Dichotomous Hill	dhl
Gamma	gam
Logistic	log
LogLogistic	lnl
LogProbit	lnp
Multistage	mst
Multistage-Cancer	msc
Probit	pro
Weibull	wei
Quantal Linear	qln

DICHOTOMOUS ALTERNATIVE MODELS

Model Type	Abbreviation
Gamma-BgDose	gmb
Logistic-BgResponse	
LogProbit-BgDose	lpb
Mutistage-BgDose	msb
Multistage-Cancer-BgDose	mcb
Probit-BgResponse	prb
Weibull-Bgdose	web

NESTED DICHOTOMOUS MODELS

Model Type	Abbreviation
Nested Logistic	nln
NCTR	nct
Rai and van Ryzin	rvr

REPEATED RESPONSE MEASURES

Model Type	Abbreviation
ToxicoDiffusion	txd

CONCENTRATION X TIME

Model Type	Abbreviation
ten Berge	ten

MULTIPLE TUMOR ANALYSIS

Model Type	Abbreviation
MS_Combo	multi

OPTIMIZATION ALGORITHMS USED IN BMDS

Two subroutines are used for all the optimizations in BMDS.

- DMNGB, written by David M. Gay, is used for all models that can be reparameterized so that BMD appears explicitly as a parameter. This routine is archived in Netlib.
- DONLP2 was written by P. Spellucci to solve optimization problems with non-linear constraints. It is used in cases where the model cannot be so reparameterized. DONLP2 is restricted to non-commercial use by the author's copyright. More information on the optimizer can be found at the author's Web site.

CONTINUOUS MODEL DESCRIPTIONS

Special Considerations for Models for Continuous Endpoints in Simple Designs

Models in this section are for continuous endpoints, such as weight or enzyme activity measures, in simple experimental designs that do not involve nesting or other complications. The models predict the mean value of the response, λ (dose), expected for a given dose.

Models for continuous endpoints require consideration of more details than do those for dichotomous endpoints in similar designs. While for dichotomous models, we normally model the incidence of adversely affected individuals, and so expect the response to increase with increasing dose, in continuous models the change in a measure is modeled without regard for "adversity", and the response may increase or decrease. Thus, just what constitutes an adverse change, and how to specify it, must be made explicit. The models in BMDS allow that specification to be made in several ways, which will be described below (BMD Computation).

Another important contrast with dichotomous models is the nature of the probability distribution of response. In dichotomous models, the nature of the experimental design guarantees that the binomial probability distribution is appropriate. There are many more options for continuous distributions, however. In the current version of BMDS, the distribution of continuous measures is assumed to be normal, with the exception of the Exponential Models, for which the user may assume either a normal or a lognormal distribution (see the section on the Lognormal Distribution below). Moreover, for all models and normally distributed data, one may assume either a constant variance (that is, the variance is the same regardless of dose group), or a variance that changes as a power function of the mean value:

$$\sigma_i^2 = \alpha[\mu(dose_i)]^\rho$$

which is the modeled variance for the *ith* dose group. the expression λ **(*dose*$_i$)** is the observed mean (from the model) for the *ith* dose group, and α (alpha) and ρ **(Rho)** are estimated parameters. This formulation allows for several commonly encountered situations. For example, if ρ= 2, then the coefficient of variation is constant, a common situation especially for biochemical measures; if ρ = 1, then the variance is proportional to the mean, which is sometimes appropriate for large counts (especially if the constant of proportionality, *k*, is 1.0). When a lognormal distribution is assumed, the Exponential Models assume a constant (log-scale) variance, equivalent to a constant coefficient of variation.

Likelihood Function

Suppose there are ***g*** doses,

$$dose_1, \ldots, dose_g$$

with ***N$_i$*** subjects per dose group, and that ***y$_{ij}$*** is the measurement for the ***jth*** subject in the ***ith*** dose group. The form of the log-likelihood function depends upon whether the variance is assumed to be constant, or to vary among doses.

For constant variance, the log-likelihood function is:

$$L = -\frac{g}{2}\ln(2\pi) - \sum_{i=1}^{g}\left[\frac{N_i}{2}\ln\sigma_i^2 + \frac{(N_i-1)s_i^2}{2\sigma_i^2} + \frac{N_i\left(\bar{y}_i - \mu(dose_i)\right)^2}{2\sigma_i^2}\right],$$

where

$$s_i^2 = \frac{\sum_{j=1}^{N_i}\left(y_{ij} - \bar{y}_i\right)^2}{N_i - 1}$$

is the sample variance for the ***ith*** dose group,

$$\bar{y}_i = \frac{\sum j = 1^{N_i} y_{ij}}{N_i - 1}$$

is the sample mean for the ***ith*** dose group, ***g*** is the number of doses, ***N$_i$*** is the number of subjects in the ***ith*** dose group, and σ^2 the variance which is same in all dose groups. Generally, σ^2 and the parameters hidden here in **λ( )** are to be estimated.

If the variance is allowed to be a power function of the mean, the log-likelihood function is:

$$L = -\sum_{i=1}^{g}\left[\frac{N_i}{2}\ln\alpha + \frac{N_i\rho}{2}\ln[\mu(x_i)] + H_i\right]$$

where

$$H_i = \frac{A_i}{2\alpha[\mu(dose_i)]^{\rho}} - \frac{B_i}{\alpha[\mu(dose_i)]^{\rho-1}} + \frac{N_i}{2\alpha[\mu(dose_i)]^{\rho-2}}$$

with

$$A_i = (N_i - 1)s_i^2 + N_i\bar{y}_i^2$$

$$B_i = N_i\bar{y}_i.$$

The upper bound for the power parameter in the Hill and power models has been (somewhat arbitrarily) set to 18. That value was selected because it represents a very high degree of curvature that should accommodate almost every dataset, even ones with very (or absolutely) flat dose-response at low doses followed by a very steep dose-response at higher doses.

If the power parameter for the Hill or power model is reported equal to 18 and the warning " *…hit a bound . . .*" appears, the parameter estimates are maximum likelihood estimates only in the restricted sense that the power parameter has been assigned a value and the other parameters are MLEs conditional on that assigned value. Such model results are not strictly comparable with others in terms of AIC. In such a case, the BMD and BMDL could depend on the choice of power parameter; thus, sensitivity analysis is indicated if one intends to rely on the reported BMD or BMDL.

BMD Computation

In the continuous models, the benchmark dose is always the dose that results in a prespecified change in the mean response. The change can be expressed in several ways:

- An absolute change in the mean (Abs. Dev.);
- A change in the mean equal to a specified number of control standard deviations (Std. Dev);
- A specified fraction of the control group mean (Rel. Dev.);
- A specified value for the mean at the BMD (i.e., not a change, but a fixed value) (Point);
- A change equal to a specified fraction of the range of the response, applicable only when the dose-response has an asymptote at high doses (Extra) [Hill and some Exponential models only].

Symbolically, these are (where δ represents the BMRF designated by the user):

$$|\mu(BMD) - \mu(0)| = \begin{cases} \delta & \text{Abs. Dev.} \\ \delta \cdot \hat{\sigma}_1 & \text{Std. Dev.} \\ \delta \cdot \mu(0) & \text{Rel. Dev.} \end{cases}$$

$$\mu(BMD) = \delta \text{ Point}$$

$$\frac{\mu(BMD) - \mu(0)}{\mu_{max} - \mu(0)} = \delta \text{ Extra}$$

BMDL Computation

BMDS currently only calculates one-sided confidence intervals, in accordance with current BMD practice. The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985). Two different approaches are followed in these models. In one, the equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

In the polynomial exponential models, it is impractical or impossible to explicitly reparameterize the dose-response model function to allow BMD to appear as an explicit parameter. For this model, the BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

Lognormal Distributions

In previous versions of BMDS, continuous data were always assumed to be normally distributed. In the current version of BMDS, for the exponential models only, the user has the option of specifying that the continuous data being analyzed are lognormally distributed. Lognormal distributions are appropriate only for data that are strictly positive and may be preferable for such data (since the normal distribution allows, in theory, both positive and negative values, no matter what the mean and standard deviation). When a lognormal distribution is specified, the models assume a constant log-scale variance, which is equivalent to an assumption of a constant coefficient of variation (CV).

The likelihood function shown above is then correct for data on the log scale (log-transformed) and is the basis for fitting the log-transformed version of the model in question. That is, if μL(dose) is the log-scale mean as a function of dose, the model being fit is μL(dose) = ln{m(dose)}, where m(dose) is the specified model (e.g., one of the exponential models parameterized as shown in the section on Exponential Models). Therefore, m(dose) will then be a description of the change in the median response as a function of dose since the anti-log of the log-scale mean is the median.

When the input data are summarized in terms of the sample mean and sample standard deviation (or standard error or variance), the exact likelihood of the data cannot be determined if the data are lognormally distributed. In such cases, BMDS gives an approximate MLE solution by estimating the log-scale sample mean and log-scale sample standard deviation for each dose group as follows:

estimated log-scale sample standard deviation (sL): sqrt{ln[1 + s2/m2]}

estimated log-scale sample mean (mL): ln[m]—sL2/2

where m and s are the reported sample mean and sample standard deviation. When individual responses are available, the user may input those values (where the input dax file will have two columns reporting the dose and the response for each experimental unit) and may request that the exact MLE solution be obtained (which the software does by first log-transforming the individual responses) or that the approximate solution using the estimates shown above be obtained (which the software does by first computing sample means and sample standard deviations). This option allows the user to compare estimates and determine the impact of the approximation or to provide consistency across data sets if some data sets have individual responses while others do not.

See also:

- Continuous Model Option Screens
- Continuous Models—Text Output
- Linear Continuous Model—Description
- Polynomial Continuous Model—Description
- Power Continuous Model—Description
- Hill Model—Description
- Exponential Continuous Models—Description
- Optimization Algorithms Used In BMDS
- Lognormal Response Option (Best Practices for Obtaining Optimal Model Convergence)

LINEAR CONTINUOUS MODEL

Model Form

The Linear model is a form of the polynomial model. The formula for the polynomial model is

$$\mu(dose) = \beta + \beta_1 dose + \beta_2 dose^2 + \cdots + \beta_n dose^n$$

The linear model is a special case of the polynomial model, with ***n*** restricted to 1.

Parameters

- **Alpha** is α from the variance model (see Continuous Model Description)
- **Rho** is ρ from the variance model (see Continuous Model Description)
- **Beta$_0$…Beta$_n$** is $\beta_1 \ldots \beta_n$; polynomial coefficients.

Special Options

Degree Poly

Degree of polynomial.

Restriction

One of “None”, “Non-Positive”, “Non-Negative”. Determines restrictions on the polynomial coefficients. Restricting them to be either non-positive or non-negative guarantees that the resulting function will be strictly decreasing, strictly increasing, or perfectly flat (when all the coefficients are zero). If the coefficients are unrestricted, more complicated shapes are possible, and, particularly as the degree of the polynomial approaches the number of dose groups minus one, the polynomial will often be quite “wavy”. When the coefficients are unrestricted and the degree is one less than the number of dose groups (for example, if there are four dose groups, including control, if the degree of the polynomial is three), then the model will exactly reproduce the means of the dose groups.

BMD Computation

The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) using numerical methods.

BMDL Computation

The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the

log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

See also:

- Continuous Models in General
- Linear Model Input File

POLYNOMIAL CONTINUOUS MODEL

Model Form

The formula for the polynomial model is

$$\mu(dose) = \beta_0 + \beta_1 dose + \beta_2 dose^2 + \cdots + \beta_n dose^n$$

Here ***n*** is the degree of the polynomial (labeled "Degree Poly." on the model option screen), and is specified by the user. The degree must be a positive integer (typically less than the number of dose groups).

The linear model is a special case of the polynomial model, with ***n*** restricted to 1.

Parameters

- **Alpha** is α from the variance model (see Continuous Model Description)
- **Rho** is ρ from the variance model (see Continuous Model Description)
- **Beta$_0$…Beta$_n$** is $\beta_1 \ldots \beta_n$; polynomial coefficients.

Special Options

Degree Poly

Degree of polynomial (maximum = 21).

Restriction

One of "None", "Non-Positive", "Non-Negative". Determines restrictions on the polynomial coefficients. Restricting them to be either non-positive or non-negative guarantees that the resulting function will be strictly decreasing, strictly increasing, or perfectly flat (when all the coefficients are zero). If the coefficients are unrestricted, more complicated shapes are possible, and, particularly as the degree of the polynomial approaches the number of dose groups minus one, the polynomial will often be quite "wavy". When the coefficients are unrestricted and the degree is one less than the number of dose groups (for example, if there are four dose groups, including control, if

the degree of the polynomial is three), then the model will exactly reproduce the means of the dose groups.

BMD Computation

The appropriate relationship for the BMR is solved (see the Continuous Models section on BMD Computation) using numerical methods.

BMDL Computation

The BMR equation (see the Continuous Models section on BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

See also:

- Continuous Model Descriptions
- Polynomial Model Input File

POWER CONTINUOUS MODEL

Model Form

The form of the Power model is:

$$\mu(dose) = \gamma + \beta \cdot (dose)\delta$$

Here, **0 < γ < 1**, **β ≥ 0**, and **18 ≥ δ > 0** with an option to restrict **δ ≥ 1**.

Parameters

- **Alpha** is α from the variance model (see Continuous Model Description)
- **Rho** is ρ from the variance model (see Continuous Model Description)
- **Control** = γ
- **Slope** = β
- **Power** = δ (The Power parameter must be a positive number ≤ 18. If Power is restricted, the number must be > 1.)

Special Options

Restrict power ≥ 1

Restrict δ ≥ 1. If δ < 1, then the slope of the dose-response curve becomes infinite at the control dose. This is biologically unrealistic, and can lead to

numerical problems when computing confidence limits, so several authors have recommended restricting $\delta \geq 1$.

BMD Computation

The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) analytically.

BMDL Computation

The equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for the slope. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

See also:

- Continuous Models in General
- Power Model Input File

HILL CONTINUOUS MODEL

Model Form

The form of the Hill model is:

$$\gamma + \frac{v \cdot d^n}{k^n + d^n}$$

Parameters

- Intercept (Control) = γ
- Dose with half-maximal change = k (must be positive number)
- Power = n (must be a positive number ≤ 18. If n is restricted, the number must be > 1.)
- Maximum change = v

Special Options

- **Restriction**: When the "Restrict n > 1" box is checked, the power parameter will be estimated to be greater than or equal to 1.

BMD Computation

The appropriate relationship for the BMR is solved analytically.

BMDL Computation

The BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

Warning

BMDL estimates from models that have an asymptote parameter (including the Hill model) can be unstable when a wide range of parameter values can give nearly identical likelihoods. One indicator of that problem is that the estimated asymptotic response is far outside the range of the observed responses. The user should consult a statistician if this behavior is seen or suspected.

See also:

- Continuous Models in General
- Hill Model Input File

EXPONENTIAL CONTINUOUS MODEL

Introduction

Dr. Wout Slob of RIVM in The Netherlands has proposed a set of nested models known as the exponential models. Currently, these models should be fit only to data having positive (mean) values.

There are four exponential models fit by BMDS and they are defined and labeled as follows.

Model Form

- Model 2: m(dose) = a*exp{sign*b*dose}
- Model 3: m(dose) = a*exp{sign*(b*dose)^d }
- Model 4: m(dose) = a*(c-(c-1)*exp{-1*b*dose})
- Model 5: m(dose) = a*(c—(c-1)*exp{-1*(b*dose)^d })

[Model 1, as defined by Dr. Slob, is the constant-mean model, called R in BMDS, which is estimated for every continuous data run.]

The parameter "sign" is the indicator of the direction of change: +1 for data trending up, -1 for data trending down. It is very important that the user correctly specify the direction of change in the data—for the Exponential Models the "automatic" choice of adverse direction has not been included. Some indicators that the wrong direction has been used for any given run include the observation that one or more models result in a flat curve fit, that optimal solutions for MLE parameters or BMDLs have not been obtained, and/or that the likelihoods associated with the models are much worse than models A1 to A3 (and are more like model R).

Parameters

For all the exponential models the following restrictions apply:

- Background Response: a (> 0)
- Slope: b (> 0)
- Asymptote Parameter: c [Models 4 and 5 only]
- c >1 for increasing data
- 0 < c < 1 for decreasing data
  Power: d (> 1) [Models 3 and 5 only]

Restrictions

There are no restrictions beyond the parameter constraints shown above for each model.

BMD Computation

The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) analytically.

BMDL Computation

The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

Warning

BMDL estimates from models that have an asymptote parameter (including Exponential models 4 and 5) can be unstable when a wide range of parameter values can give nearly identical likelihoods. One indicator of that problem is that the estimated asymptotic response is far outside the range of the observed responses. The user should consult a statistician if this behavior is seen or suspected.

See also:

- Continuous Models in General
- Exponential Model Input File
- Unique Options for Exponential Models

DICHOTOMOUS MODEL DESCRIPTIONS

Special Considerations for Models for Dichotomous Endpoints in Simple Designs

BMDS includes in this category models for dichotomous endpoints in which the observations are independent of each other. In these models, the dose-response model provides the probability that an animal will have an adverse response at a given dose. The actual number of animals that have an adverse response is assumed to be binomially distributed.

An example of such a dataset is a study in which adult animals are exposed to different concentrations of a toxicant and then evaluated for the presence of liver toxicity. For models for dichotomous endpoints in which the responses are nested (for example, pups in litters, and litters nested within doses), see the section Nested Model Descriptions.

BMDS contains ten models for dichotomous endpoints (the Probit, Log-Probit, Logistic, Log-Logistic, Weibull, Quantal Linear, Gamma, Multistage, and Multistage-Cancer models). They may all be written in the form:

$$\text{Prob}\{response\} = \gamma + (1 - \gamma)F(dose; \alpha, \beta, \ldots)$$

Here ***F*(*dose*; α, β, …)** is a cumulative distribution function and **γ, α, β, …**, are parameters to be estimated using maximum likelihood methods. Sometimes **Prob{*response*}** is written as **P[*dose*; γ, α, β, …]** to indicate the relationship between the response probability and the dose as well as parameters. When the function ***F*(*dose*; α, β, …)** approaches zero as dose approach zero, the parameter γ represents the background incidence. In the Logistic and Probit models, ***F*(*0*)** is not zero, unlike in the Log-Logistic and Log-Probit models. In these models, γ is set to 0.

Special Options for Models

In addition to the options that are available to all dichotomous models, there may be model-specific options. Generally, these are options to restrict the legal range

of a parameter or set of parameters. The range of a parameter may be restricted for two reasons:

- the slope of the dose-response curve becomes infinite at a dose of 0 if the parameter falls below 1, so that the default is to restrain that parameter to be at least 1, or
- the quantal polynomial dose-response curve can become non-monotonic if the coefficients are allowed to be negative, often resulting in the curve looking "wavy", so the default is to restrict the coefficients to be non-negative.

The applicable special options are listed in the sections for the specific models.

Likelihood Function

All models in the current version of BMDS are fit using maximum likelihood methods. This section describes the likelihood function used to fit the dichotomous models.

Suppose we employ k doses:

$$dose_1, dose_2, \ldots dose_k$$

and the total number of s and number of responding s in each dose group are

$$N_1, N_2, \ldots N_k$$

and, respectively,

$$n_1, n_2, \ldots n_k$$

The distribution of n_i is assumed to be binomial with probability

$$p_i = p(dose_i; \Theta), i = 1, 2, \ldots, k$$

where Θ is a vector of parameters. Then the log-likelihood function L can be written as

$$L = \sum_{i=1}^{k} L_i(N_i, n_i, dose_i;\ \Theta)$$

where

$$L_i = n_i \ln(p_i) + (N_i - n_i) \ln(1 - p_i)\,, i = 1,2, \ldots, k.$$

The upper bound for the power parameter in the gamma and Weibull models, and the slope parameter for the log-probit and log-logistic models, has been (somewhat arbitrarily) set to 18. That value was selected because it represents a very high degree of curvature that should accommodate almost every data set,

even ones with very (or absolutely) flat dose-response at low doses followed by a very steep dose-response at higher doses.

If the power parameter for the gamma or Weibull model, or the slope parameter for the log-probit or log-logistic model, is reported equal to 18 and the warning "…hit a bound…" appears, the parameter estimates are maximum likelihood estimates only in the restricted sense that the power parameter has been assigned a value and the other parameters are MLEs conditional on that assigned value. Such model results are not strictly comparable with others in terms of AIC. In such a case, the BMD and BMDL could depend on the choice of power parameter; thus, sensitivity analysis is indicated if one intends to rely on the reported BMD or BMDL.

BMD Computation

The BMD is computed as a function of the parameters of the model, which must have already been estimated. The BMDs for dichotomous models are expressed as the dose that would give an (estimated) increase in incidence of x% above the control incidence (where x is often in the range of 1 to 10 percent). This increase in incidence is referred to here as the "BMRF", for benchmark response factor. Note that, although the word "response" is used here, we are really talking about an increase of the incidence over the control incidence (added risk). The actual response associated with the BMR, will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response associated with the BMR one must solve for P(d) in the equation for added or extra risk.

Two formulations for computing the excess over background are in common use, the extra risk model and the additional risk model. In the extra risk model,

$$BMR = \frac{p(BMD;\gamma,\alpha,\beta,\dots) - p(0;\ \gamma,\alpha,\beta,\dots)}{1 - p(0;\ \gamma,\alpha,\beta,\dots)}$$

while in the additional risk model,

$$BMR = \ p(BMD;\gamma,\alpha,\beta,\dots) - p(0;\ \gamma,\alpha,\beta,\dots).$$

The equation appropriate to the risk type formulation that the user requests is solved to get the BMD for a specific model and dataset. Details of this computation are included in the descriptions of the models.

BMDL Computation

BMDS currently calculates one-sided confidence intervals, in accordance with current BMD practice.

Note The Multistage and Multistage-Cancer models also calculate one-sided upper confidence limits.

The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985). Two different approaches are followed in these models. In one, the equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

In a few models, it is impractical or impossible to explicitly reparameterize the dose-response model function to allow BMD to appear as an explicit parameter. For these models, the BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

See also:

- Dichotomous Model Option Screens
- Dichotomous—Text Output
- Gamma Model—Description
- Logistic Model—Description
- Log-Logistic Model—Description
- Multistage and Multistage-Cancer Model—Description
- Probit Model—Description
- Log-Probit Model—Description
- Quantal Linear Model—Description
- Weibull Model—Description
- Optimization Algorithms Used In BMDS

GAMMA MODEL

Model Form

The Gamma Model formula is:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma + (1-\gamma)\cdot\frac{1}{\Gamma(\alpha)}\int_0^{\beta dose} t^{\alpha-1}\mathrm{e}^{-t}dt$$

Here, **0 < γ < 1**, **β ≥ 0**, and **18 ≥ α > 0** with an option to restrict **α ≥ 1**.

Parameters

- "background" is γ (If specified or initialized, the background parameter must be a number > 0 and < 1.)
- "power" is α (If specified or initialized, the Power parameter must be a positive number < 18. If Power is restricted, the number must be > 1.)
- "slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Restrict power ≥ 1

Restrict **α ≥ 1**. If **α < 1**, then the slope of the dose-response curve becomes infinite at the control dose. This is biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting **α ≥ 1**

BMD Computation

Let

$$G(x;\alpha) = \frac{1}{\Gamma(\alpha)}\int_0^x t^{\alpha-1}\mathrm{e}^{-t}dt$$

be the incomplete Gamma function and

$$G^{-1}(\cdot;\alpha)$$

be its inverse function. Then

$$BMD = \begin{cases} \dfrac{G^{-1}(BMR;\alpha)}{\beta} & \text{extra risk} \\ \dfrac{G^{-1}\left(\dfrac{BMR}{1-\gamma};\alpha\right)}{\beta} & \text{additional} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter β, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Models Description
- Gamma-hit Model Input File

LOGISTIC MODEL

Model Form

The form of the probability function for the Logistic model is

$$\text{Prob}\{response\} = p(dose; \alpha, \beta) = \frac{1}{1 + \text{e}^{-(\alpha+\beta dose)}}$$

Parameters

- "intercept" is α
- "slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Special Options

- None.

BMD Computation

The BMD estimate for the Logistic model is defined implicitly by the following equation. An iterative numerical method is used to determine the value of BMD:

$$BMD = -\frac{\ln\left(\frac{1-Z}{1+Ze^{-\alpha}}\right)}{\beta}$$

where

$$Z = \begin{cases} BMR \text{ x } \frac{1+e^{-\alpha}}{e^{-\alpha}} \text{added risk} \\ BMR \text{ extra risk} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter α, which is then replaced in the original model equations.

This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

Notes

Occasionally, the following error message may appear for this model: "BMDL computation is at best imprecise for these data." This is a flag that convergence for the BMDL was not "successful" in the sense that the required level of convergence (< 1e-3 relative change in the target function by the time the optimizer terminates) has not been achieved.

See also:

- Dichotomous Model Descriptions
- Logistic and Log-Logistic Models Input File Format

LOG-LOGISTIC MODEL

Model Form

The form of the probability function for the Log-Logistic model is

if dose > 0:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + \frac{1-\gamma}{1+\text{e}^{-(\alpha+\beta\ln(dose))}},$$

and if dose = 0:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma;$$

Here, **0 < γ < 1**, $\beta \geq 0$, and **18 ≥ α > 0** (with an option to restrict $\alpha \geq 1$).

Parameters

- "background" is γ (If specified or initialized, the background parameter must be a number > 0 and ≤ 1.)
- "intercept" is α
- "slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Special Options

- **Restrict slope > 1**: If the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation

The BMD estimate for the Log-Logistic model is:

$$\ln(BMD) = \begin{cases} \dfrac{\ln\left(\frac{BMR}{1-BMR}\right) - \alpha}{\beta} & \text{extra risk} \\ \dfrac{\ln\left(\frac{BMR}{1-\gamma-BMR}\right) - \alpha}{\beta} & \text{added risk.} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter α, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Model Descriptions
- Logistic and Log-Logistic Models Input File Format

MULTISTAGE AND MULTISTAGE-CANCER MODEL

Model Form

The Multistage and Multistage-Cancer Model formula is:

$$\text{Prob}\{response\} = p(dose; \gamma, \beta_1, \ldots, \beta_n) = \gamma + (1-\gamma) \cdot \left(1 - e - \sum_{j=1}^{n} \beta_j dose^j\right)$$

Here, **0 < γ < 1**, and there is an option to restrict **β_i > 0** for all ***i*s.** The degree of the polynomial is *n*. The Multistage-Cancer model is exactly the same as the Multistage model except that the β parameters are always restricted to be positive (the Multistage model allows them to be positive or negative).

Parameters

- **"**Background" is γ (If specified or initialized, the background parameter must be a number > 0 and < 1.)
- Dose Coefficients (Beta$_1$ …Beta$_n$) are β>sub>1 …β_n

Special Options

- **Degree Poly**: The maximum degree polynomial to fit (maximum = 23). The degree must be a positive integer (typically less than the number of dose groups).
- **Restrict Betas >= 0**: When this box is checked, the polynomial coefficients are restricted to be non-negative. This guarantees that the dose-response function will either be perfectly flat or always increasing, with no "bumps". This

restriction option is not available for the Multistage-Cancer model because it is always implemented for that model.

BMD Computation

There is no general analytic form for the BMD in terms of the BMR and the estimated model parameters for the multistage model. Instead, BMD is the root of the equation

$$\beta_1 BMD + \cdots + \beta_n BMD^n + \ln(1 - A) = 0$$

where

$$A = \begin{cases} BMR \text{ extra risk} \\ \dfrac{BMR}{1-\gamma} \text{ additional risk} \end{cases}$$

BMDL Computation

The BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\frac{\chi^2_{1,1-2\alpha}}{2}$$

See also:

- Dichotomous Model Descriptions
- Multistage (Polynomial) Model Input File

PROBIT MODEL

Model Form

The form of the probability function for the Probit model is

$$\text{Prob}\{response\} = p(dose, \alpha, \beta) = \Phi(\alpha + \beta_{dose}),$$

where

$$\Phi(x) = \int_{-\infty}^{x} \phi(t)dt$$

and

$$\phi(t) = \frac{1}{\sqrt{2\pi}} e^{-t^2/2}$$

(that is, **ø** is the standard normal density function, and **ϕ** is the normal distribution function), **18** ≥ β ≥ **0** (with an option to restrict β ≥ **1**).

Parameters

- "intercept" is α
- "slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Special Options

- **Log of Dose**: This results in the Log-Probit model.
- **Restrict slope > 1** (Log-Probit only): if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.
- **BMD Computation**

The BMD estimate for the Probit model is defined implicitly by the following equation. An iterative numerical method is used to determine the value of BMD:

$$BMD = \begin{cases} \dfrac{\Phi^{-1}\left(BMR[1-\Phi(\alpha)]+\Phi(\alpha)\right)-\alpha}{\beta} & \text{extra risk} \\ \dfrac{\Phi^{-1}\left(BMR+\Phi(\alpha)\right)-\alpha}{\beta} & \text{added risk} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter α, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Model Descriptions
- Probit and Log-Probit Models Input Files

LOG-PROBIT MODEL

Model Form

The form of the probability function for the Log-Probit model is, if dose > 0:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma + (1-\gamma)\Phi(\alpha+\beta\ln(dose)),$$

and if dose = 0:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma;$$

where

$$\Phi(x) = \int_{-\infty}^{x} \phi(t)dt$$

and

$$\phi(t) = \frac{1}{\sqrt{2\pi}} e^{-t^2/2}$$

(that is, **ø** is the standard normal density function, and ϕ is the normal distribution function), **0 < γ < 1, 18 ≥ β ≥ 0** (with an option to restrict **β ≥ 1**).

Parameters

- "background" is γ (If specified or initialized, the background parameter must be a number > 0 and < 1.)
- "intercept" is α
- "slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Special Options

For the log-probit model, the slope of the model will approach zero as dose approaches zero. However, depending on the data and parameter estimates, the slope for the log-probit model, for some relatively low doses perhaps less than those corresponding to the BMR, the slope can be quite steep, which may be manifested in terms of a relatively low value for the BMDL (or perhaps an "NA" result for the BMDL if this causes convergence problems because the steepness entails BMDL estimates that get very small).

BMD Computation

The BMD estimate for the Log-Probit model is:

$$\ln(BMD) = \begin{cases} \dfrac{\Phi^{-1}(BMR) - \alpha}{\beta} & \text{extra risk} \\ \dfrac{\Phi^{-1}\left(\dfrac{BMR}{1-\gamma}\right) - \alpha}{\beta} & \text{added risk.} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter α, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Model Descriptions
- Probit and Log-Probit Models Input Files

QUANTAL LINEAR MODEL

Model Form

The Quantal Linear model is a form of the Weibull model. The Weibull Model formula is:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$$

The Quantal Linear model results from setting α equal to 1 in the Weibull Model.

Parameters

- "Background" is γ (If specified or initialized, the background parameter must be a number > 0 and < 1.)
- "Slope" is β (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)
- "Power" is α **= 1**

Special Options

None

BMD Computation

The BMD estimate for the Weibull model is:

$$BMD = \begin{cases} \left[\frac{-\ln(1-BMR)}{\beta}\right]^{\frac{1}{\alpha}} & \text{extra risk} \\ \left[\frac{-\ln(1-\frac{BMR}{1-\gamma})}{\beta}\right]^{\frac{1}{\alpha}} & \text{additional risk} \end{cases}$$

BMD estimates for the quantal linear model is found by substituting 1 for α.

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter β, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Model Descriptions
- Quantal Linear Model Input File

WEIBULL MODEL

Model Form

The Weibull Model formula is:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + (1 - \gamma)(1 - e^{-\beta dose^{\alpha}})$$

Here, **0 < γ < 1**, **β ≥ 0**, and **18 ≥ α > 0** with an option to restrict **α ≥ 1**.

Note The Quantal Linear model results from setting α equal to 1 in the Weibull Model.

Parameters

- "Background" is γ (If specified or initialized, the background parameter must be a number > 0 and < 1.)
- "Slope" is β (If specified or initialized, the Slope parameter must be a number > 0.)
- "Power" is α (If specified or initialized, the Power parameter must be a non-negative number < 18. If Power is restricted, the number must be ≥ 1. If Power is unrestricted, the number must be greater than or equal to the value entered for the Lower Bound on Power (strictly greater than that bound if it is 0).

Special Options

- **Restrict power ≥ 1**: Restrict α ≥ 1. If α < 1, then the slope of the dose-response curve becomes infinite at the control dose. This is biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting α ≥ 1.

BMD Computation

The BMD estimate for the Weibull model is:

$$BMD = \begin{cases} \left[\frac{-\ln(1 - BMR)}{\beta}\right]^{\frac{1}{\alpha}} & \text{extra risk} \\ \left[\frac{-\ln(1 - \frac{BMR}{1 - \gamma}}{\beta}\right]^{\frac{1}{\alpha}} & \text{additional risk} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter β, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

See also:

- Dichotomous Model Descriptions
- Weibull Model Input File

DICHOTOMOUS ALTERNATIVE MODEL DESCRIPTIONS

Model Form

The form of the probability function for the Dichotomous Hill model is:

when d = 0, P[0, v, g, a, b] = v * g

Parameter constraints:

- 0 < g < 1
- 0 < v < 1
- b > 0

Parameters

- "v" is the maximum probability of response predicted by the model
- "g" multiplied by **v (v*g)** is the background estimate of the maximum probability of response
- "intercept" is **a**
- "slope" is **b** (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)
- BMR must be a number > 0 and < 1

Special Options

- **Restrict Slope ≥ 1**: if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation

The BMD estimate for the Dichotomous Hill model is defined by the following equation.

Added risk:

$$BMD = e\frac{-a - Log\left[-\frac{BMR - v + g * v}{BM}\right]}{b}$$

Extra risk:

$$BMD = e\frac{-a - Log\left[-\frac{BMR - v + g * v - BMR * g * v}{BMR(-1 + g * v)}\right]}{b}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter.

DICHOTOMOUS HILL MODEL

Model Form

The form of the probability function for the Dichotomous Hill model is:

$$\text{Prob}\{response\} = v * g + (v - v * g)/[1 + \exp(-a - b * \ln(dose))]$$

when d = 0, Prob{response} = v * g

Parameters

- "v" is the maximum probability of response predicted by the model **(0 < v ≤ 1)**
- "g" multiplied by **v (v*g)** is the background estimate of the probability of response (the parameter g must be a number > 0 and < 1)
- "intercept" is **a**
- "slope" is **b** (If specified or initialized, the Slope parameter must be a number > 0. If Slope is restricted, the number must be > 1.)

Special Options

- **Restrict Slope > 1**: if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation

The BMD estimate for the Dichotomous Hill model is defined by the following equation.

Added risk:

$$BMD = e\frac{-a - \log\left[-\frac{BMR - v + g * v}{BM}\right]}{b}$$

Extra risk:

$$BMD = e\frac{-a - \log\left[-\frac{BMR - v + g * v - BMR * g * v}{BMR(-1 + g * v)}\right]}{b}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter **α**, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See the section on Dichotomous Models' BMDL Computation for further details.

Notes

Occasionally, the following error message may appear for this model: "BMDL computation is at best imprecise for these data." This is a flag that convergence for the BMDL was not "successful" in the sense that the required level of convergence (< 1e-3 relative change in the target function by the time the optimizer terminates) has not been achieved.

QUANTAL MODELS WITH BACKGROUND DOSE PARAMETER

Users should consult the Help file or this user guide for a specific model for details on that model. With a few obvious changes, those details apply also to models with a background dose parameter.

Two Forms of Each Quantal Model

For each of four 'traditional' quantal models in BMDS (multistage, log probit, gamma, and Weibull), alternative models were developed that incorporate a background dose parameter in place of a background response parameter. Such a model was also developed for the log logistic function but is not included in this release for technical reasons[1].

The "cancer model" is a version of the multistage model for which the user cannot relax the restriction on coefficients that requires them to be non-negative,

1 The log-logistic model with background dose parameter has an especially "flat" log-likelihood surface, making it difficult, for some datasets, for the software to converge to a maximum likelihood solution and especially difficult to solve the BMDL. In general, that model often fails to converge on a BMDL solution when the control response is larger than approximately 0.2—0.4.

and which reports the "cancer slope factor" (calculated as BMR/BMDL). A new version of this model is provided with a background dose parameter.

The original logistic and probit models (without log-transformation of the dose) implicitly allow for a background dose effect, although a background dose parameter is not explicitly estimated. These models do not have a background response parameter. Thus, new versions of these models are provided which add an explicit background response parameter γ, increasing the number of parameters from two to three for these new models.

Thus, for each type of quantal model in BMDS, there are now two alternative versions available, one with a background dose parameter and another with a background response parameter.

The alternative forms of model can be represented as follows:

Background response parameter, γ: $\mathrm{P}(\beta, \mathrm{x}, \gamma) = \gamma + (1-\gamma) * \mathrm{F}\{\beta, \mathrm{x}\}$

Background dose parameter, η: $\mathrm{P}(\beta, \mathrm{x}, \eta) = \mathrm{F}\{\beta, (\mathrm{x}+\eta)\}$

Here, F{β, x} represents the functional form specific to each model (multistage, logistic, etc.). F{β, x} is a probability distribution function taking values between 0 and 1 for positive dose values. For more details, see Table 27. In the background dose version of a model, parameter γ is dropped and the parameter η is added.

Table 27: *Comparison of current BMDS quantal models with new models allowing a background dose or background response parameter.*

Model Name[1]	Functional Form of the Model	Explicit Background Parameter	Low Dose Linearity?	# Parameters
Multistage[2]	$\gamma + (1-\gamma)[1 - \exp\{-\sum_{f=1}^{k} \beta_j X^j\}]$	γ	Yes, if $\beta_1 > 0$ No if $\beta_1 = 0$	1+k
multistage_bgd	$1 - \exp\{-\sum_{f=1}^{k} \beta_j (X+\eta)^j\}$	η	Yes	1+k
Logistic	$[1 + \exp\{-(\alpha + \beta \mathrm{X})\}]^{-1}$	None	Yes	2
logistic_bgr	$\gamma + (1-\gamma)[1 + \exp\{-(\alpha + \beta \mathrm{X})\}]^{-1}$	γ	Yes	3
Probit	$\Phi\{\alpha + \beta \mathrm{X}\}$	None	Yes	2
probit_bgr	$\gamma + (1-\gamma)\, \Phi\{\alpha + \beta \mathrm{X}\}$	γ	Yes	3
Log_logistic	$\gamma + (1-\gamma)[1 + \exp\{-(\alpha + \beta \log\{\mathrm{X}\})\}]^{-1}$	γ	No	3
log_logistic_bgd	$[1 + \exp\{-(\alpha + \beta \log\{\mathrm{X}+\eta\})\}]^{-1}$	η	Yes	3
Log_probit	$\gamma + (1-\gamma)\, \Phi\{\alpha + \beta \log\{\mathrm{X}\}\}$	γ	No	3

Model Name[1]	Functional Form of the Model	Explicit Background Parameter	Low Dose Linearity?	# Parameters
log_probit_bgd	$\Phi\{\alpha + \beta \log\{X + \eta\}\}$	η	Yes	3
Gamma	$\gamma + (1-\gamma)\left[\int_{-0}^{\beta x} t^{\alpha-1}e^{t}dt\right] / \Gamma(\alpha)$	γ	No[3]	3
gamma_bgd	$G(\beta(d+\eta),\alpha)/\Gamma(\alpha)$ G is the incomplete gamma function	η	Yes	3
Weibull	$\gamma + (1-\gamma)[1-\exp\{-\beta X^{\alpha}\}]$	γ	No[3]	3
weibull_bgd	$[1-\exp\{-\beta(X+\eta)^{\alpha}\}]$	η	Yes	3

[1] Names in regular type denote modules (i.e., *.exe files) that currently exist within BMDS. Names in italics denote alternative forms of the models with a new background parameter.

[2] The cancer model is identical to the multistage model except that $\beta \geq 0$ is enforced and the cancer slope factor is reported.

[3] If power parameter is > 1, slope $\rightarrow$ 0 as dose $\rightarrow$ 0; if power parameter is < 1, slope $\rightarrow \infty$ as dose $\rightarrow$ 0.

Confidence Limits for the Benchmark Dose (BMD)

The new models report both lower and upper confidence limits for the benchmark dose, that is, BMDL and BMDU. The confidence level selected by the user applies to a one-sided confidence limit (as for all the quantal models). Thus, if the user selects a 95% confidence level, "*Confidence level = 0.95*" is reported in the *.out file with the BMD, BMDL, and BMDU. This confidence level applies to a one-sided interval for BMD, e.g., [BMDL, ∞]. If the user reports the two-sided interval [BMDL, BMDU], the appropriate confidence level in this example is 90%; in general, if the user selects a confidence level 1-α, the two-sided interval has confidence level 1–2α.[2]

Parameter Constraints

This section applies to BMDS quantal models generally and is not specific to the new versions of those models. Two sorts of constraints are applicable to the quantal models: natural constraints, which limit parameters to those values permitting 0 ≤ P(dose; β, η) ≤ 1, and user-selectable constraints. The latter will

2 In some cases, the 2-sided confidence limits may have coverage larger than stated (e.g., greater than 95%), because in some cases they may bound a collection of confidence regions rather than an unbroken interval.

default to standard settings in BMDS with no need for user actions. Examples of user-selectable constraints are restrictions on the multistage coefficients, which normally are required to be non-negative in order to provide a monotonically increasing dose response function, and a restriction on the power parameter of the gamma and Weibull models, which BMDS requires by default to be no smaller than 1. Natural parameter constraints are shown in the following table. Advice and observations on user-selectable constraints are provided in the Benchmark Dose Technical Guidance document.

Table 28: *Natural parameter constraints in BMDS quantal models*

Model Name[1]	Functional Form of the Model	Parameter Constraints
Multistage[2]	$\gamma + (1-\gamma)[1-\exp\{-\sum_{f=1}^{k}\beta_j X^j\}]$	$0 \le \gamma \le 1$
multistage_bgd[2]	$1-\exp\{-\sum_{f=1}^{k}\beta_j (X+\eta)^j\}$	$\eta \ge 0$
Logistic	$[1+\exp\{-(\alpha+\beta X)\}]^{-1}$	$-\infty < \alpha < +\infty, \beta \ge 0$
logistic_bgr	$\gamma + (1-\gamma)[1+\exp\{-(\alpha+\beta X)\}]^{-1}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $0 \le \gamma \le 1$
Probit	$\Phi\{\alpha+\beta X\}$	$-\infty < \alpha < +\infty, \beta \ge 0$
probit_bgr	$\gamma + (1-\gamma)\,\Phi\{\alpha+\beta X\}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $0 \le \gamma \le 1$
Log_logistic	$\gamma + (1-\gamma)[1+\exp\{-(\alpha+\beta\log\{X\})\}]^{-1}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $0 \le \gamma \le 1$
log_logistic_bgd	$[1+\exp\{-(\alpha+\beta\log\{X+\eta\})\}]^{-1}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $\eta \ge 0$
Log_probit	$\gamma + (1-\gamma)\,\Phi\{\alpha+\beta\log\{X\}\}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $0 \le \gamma \le 1$
log_probit_bgd	$\Phi\{\alpha+\beta\log\{X+\eta\}\}$	$-\infty < \alpha < +\infty, \beta \ge 0$ $\eta \ge 0$
Gamma	$\gamma + (1-\gamma)\left[\int_{-0}^{\beta x} t^{\alpha-1}e^{t}dt\right] / \Gamma(\alpha)$	$\alpha > 0, \beta \ge 0$ $0 \le \gamma \le 1$
gamma_bgd	$G(\beta(d+\eta),\alpha)/\Gamma(\alpha)$ G is the incomplete gamma function	$\alpha > 0, \beta \ge 0$ $\eta \ge 0$
Weibull	$\gamma + (1-\gamma)[1-\exp\{-\beta X^{\alpha}\}]$	$\alpha > 0, \beta \ge 0$ $0 \le \gamma \le 1$
weibull_bgd	$[1-\exp\{-\beta(X+\eta)^{\alpha}\}]$	$\alpha > 0, \beta \ge 0$ $\eta \ge 0$

[1] Names in regular type denote modules (i.e., *.exe files) that currently exist within BMDS. Names in italics denote modules that are new to BMDS and represent alternative forms of the models with a new background parameter.

[2] The cancer model is identical to the multistage model except that $\beta_j \ge 0$ is enforced and the cancer slope factor is reported.

In some cases, BMDS software will report that a parameter has "*… hit a bound implied by some inequality constraint and thus has no standard error.*" In that case, the printed parameter estimate will equal some natural or user-selectable

constraint (for example, β = 0 for multistage, or power α=1 for gamma[3]). In such cases, the Wald confidence intervals for the other parameters are not even asymptotically correct.[4] The 2-sided profile-likelihood confidence intervals for the BMD and Extra or Added Risk are asymptotically correct in such cases[5]. (However, whether or not a boundary has been "hit", a 1- sided profile-likelihood confidence interval may not have the nominal coverage—if the nominal coverage is 1-α, the asymptotic coverage for BMDL could be anything between 1 and 1–2α.)

The upper bound for the power parameter in the gamma and Weibull models has been (somewhat arbitrarily) set to 18. That value was selected because it represents a very high degree of curvature that should accommodate almost every data set, even ones with very (or absolutely) flat dose-response at low doses followed by a very steep dose-response at higher doses.

If the power parameter for the gamma or Weibull models is reported equal to 18 and the warning "… hit a bound …" appears, the parameter estimates are maximum likelihood estimates only in the restricted sense that the power parameter has been assigned a value and the other parameters are MLEs conditional on that assigned value. Such model results are not strictly comparable with others in terms of AIC. In such a case, the BMD and BMDL could depend on the choice of power parameter; thus, sensitivity analysis is indicated if one intends to rely on the reported BMD or BMDL.

Origin and Properties of Background Parameters

The background response parameter has been said to represent "… independent action between the chemical and the background." (NRC, 1980), or, in the case of cancer, "… carcinogens that cause a response of cancer in a way that is completely independent of the mechanisms by which the primary carcinogen causes a response." (Crump et al., 1976). Thus, it has also been called an independent background (Crump et al., 1976; Hoel, 1980). The background dose parameter has been said to represent additivity between the applied dose of a chemical and the background (NRC, 1980), or to represent "… carcinogens (including spontaneous biochemical accidents) that somehow act in conjunction with the primary carcinogen …" (Crump et al., 1976). Thus, it has also been termed an additive background (Crump et al., 1976; Hoel, 1980).

3 There is also an arbitrary upper bound of 18 for the power parameter for the gamma and Weibull models.

4 See G. Molenberghs and G. Verbeke (2007) American Statistician 61: 22–27; B. Sinha et al. technical report at http://www.math.umbc.edu/~kogan/technical_papers/index2007.html.; Self, S.S. and K-Y. Liang (1987) Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions, J.Am. Stat. Assoc. 82: 605–610.

5 B. Sinha et al. technical report at http://www.math.umbc.edu/~kogan/technical_papers/index2007.html.

Models with a background dose parameter will have an approximately linear response to dose at very low doses (Crump et al., 1976). Only some of the original quantal models will behave in this way (see Table 27). The specification of the background term can have a substantial influence over risk estimates made well below the range of experimental doses (Krewski and van Ryzin, 1981; NRC, 1980). The original logistic and probit models (*without* log-transformation of the dose) implicitly allow for a background dose effect, although a background dose parameter is not explicitly estimated, and these models exhibit low-dose linearity. The new versions of these models provide an explicit background response parameter, and also exhibit low-dose linearity.

Model Behavior in Relation to Background Parameter

The effects of the two sorts of background parameters, γ and η, are illustrated for the log-probit models:

$$\mathrm{P}(\mathrm{dose};\ \gamma,\alpha,\beta) = \gamma + (1-\gamma)\Phi(\alpha + \beta\log\{\mathrm{X}\})$$

$$\mathrm{P}(\mathrm{dose};\eta,\alpha,\beta) = \Phi(\alpha + \beta\log\{\mathrm{X}+\eta\})$$

Models with a background response parameter can represent the functional shape of F(dose; β) starting from a "floor" at P(0) = γ (Figure 1). The response curve may appear sigmoidal, concave ("supralinear"), convex ("sublinear") or nearly linear, depending on the values of the other parameters.

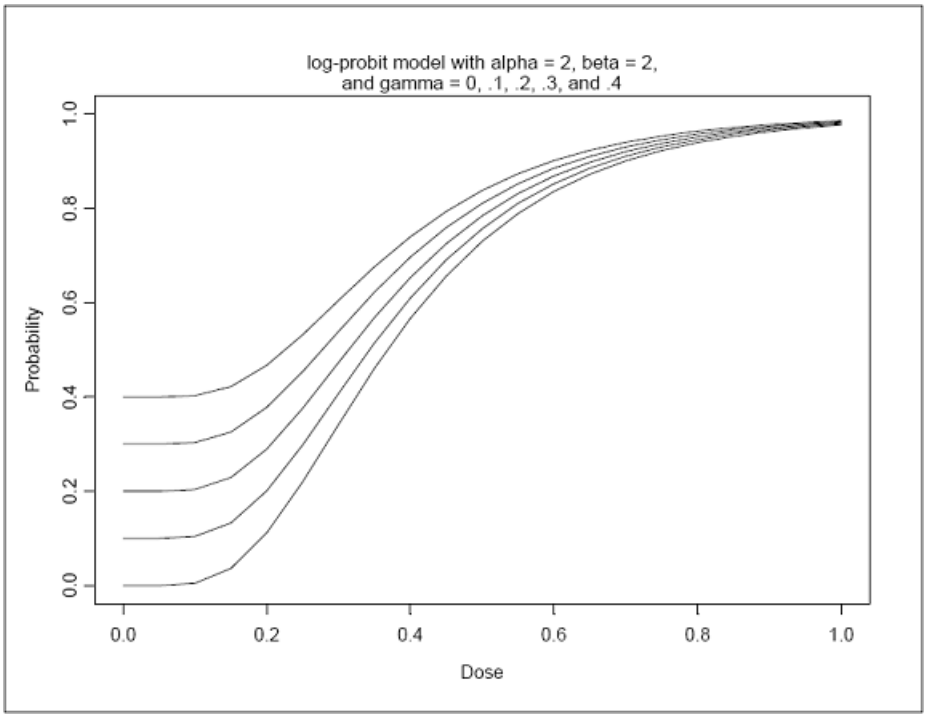


Figure 1.—*Log-probit model with background response term, P(dose; γ, α, β) = γ + (1-γ) ϕ{α + β*log(X)}. Here α = 2, β = 2, and γ is varied from 0 to 0.4.*

Models with a background parameter additive to dose (η) can shift the response curve left or right (Figure 2), for fixed α (intercept) and β (slope). The background dose model can successfully fit datasets that appear concave ("supralinear"), appearing as if the response had been truncated on the left. Figure 2 also suggests that the background dose model may have difficulty fitting a convex or sigmoidal data pattern that begins with a high control response, but may be successful in fitting a linear to concave (supralinear) response that begins with a high response at zero dose. (In Figure 2, the other two parameters are fixed; however, experience with maximum likelihood fitting of various datasets suggests that these qualitative generalizations are correct).

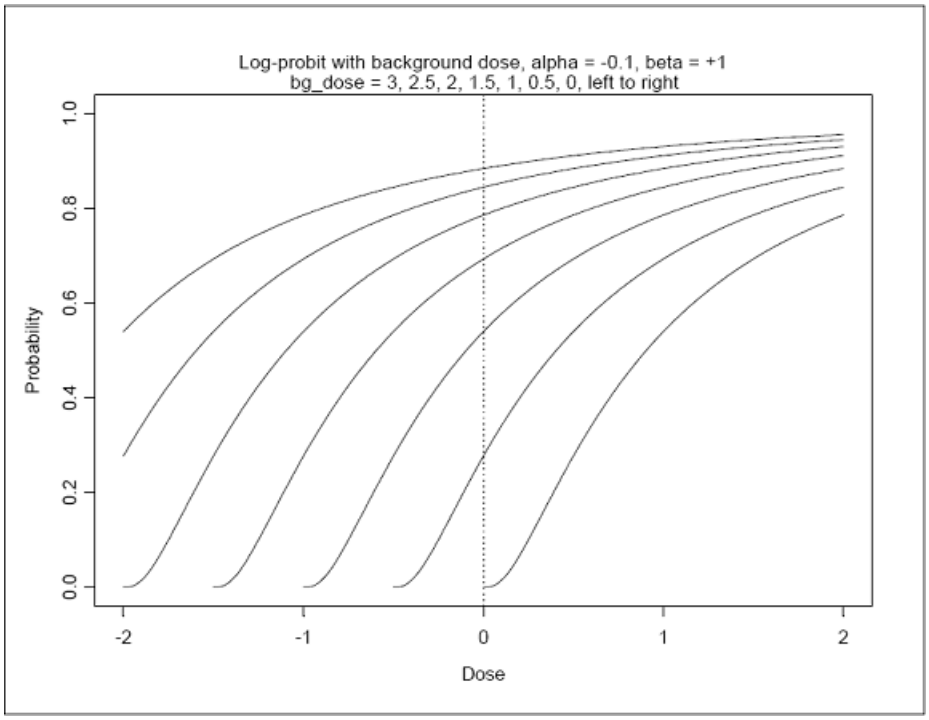


Figure 2.—*Log-probit model with background dose term.*

The background-dose parameter (η) was varied, taking values of 3 to 0 from left to right. For this plot, α = -0.1 and β = 1. This illustrates how increasing the background dose parameter shifts the response curve leftward (observed doses would of course be non-negative; the horizontal axis was extended to negative doses to illustrate the functional forms of these models).

Figure 3 shows an example of fitting an artificial dataset generated using a known log-probit function. In this case, the two log-probit models fit equally well. They differ almost two-fold in BMDL, and of course one is linear at low doses and the other is sublinear. Figure 4 shows an example of fitting log-probit models to data generated using a log-logistic function, illustrating how the two models, differing in background parameter, will differ in the low-dose region.

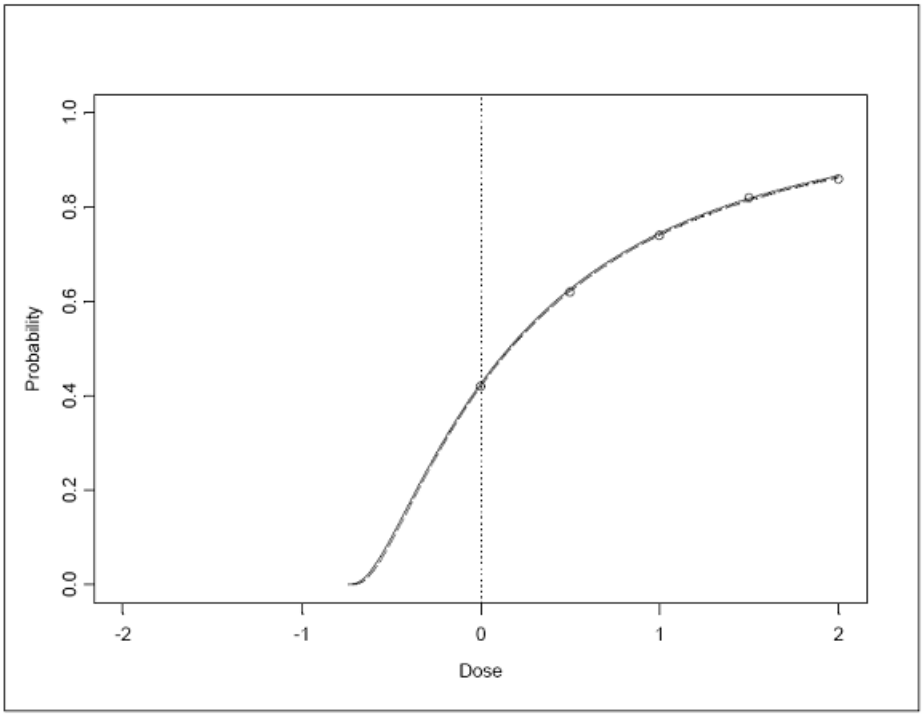


Figure 3.—*Log-probit model with background dose term fitted to data*.

The model P = $\phi(\alpha + \beta^*(\log(\text{dose} + \eta))$, with parameters $\eta = 0.75$, $\alpha = 0.1$, $\beta = 1$, was used to generate probabilities for doses 0, 0.5, 1.0, 1.5, and 2.0. Expected numbers out of 50 animals were rounded to the nearest integer, giving numbers affected of 21, 31, 37, 41, and 43. The model was fitted to these artificial data, yielding estimated parameters $\eta = 0.727918$, a = 0.108666, b = 0.982273. The solid line shows the exact model used to generate the data, and the dashed line shows the estimated model. Circles show the data as observed proportions of 50 animals affected. Goodness of fit statistics: Chi-square(2) = 0.01, P-value = 0.9929. The log-probit model with background response was also fitted (Chi-square(2) = 0.01, P-value = 0.9942). These models predicted BMDL values of 0.0216005 and 0.0126529, respectively, for extra risk 0.1 at the 95% level.

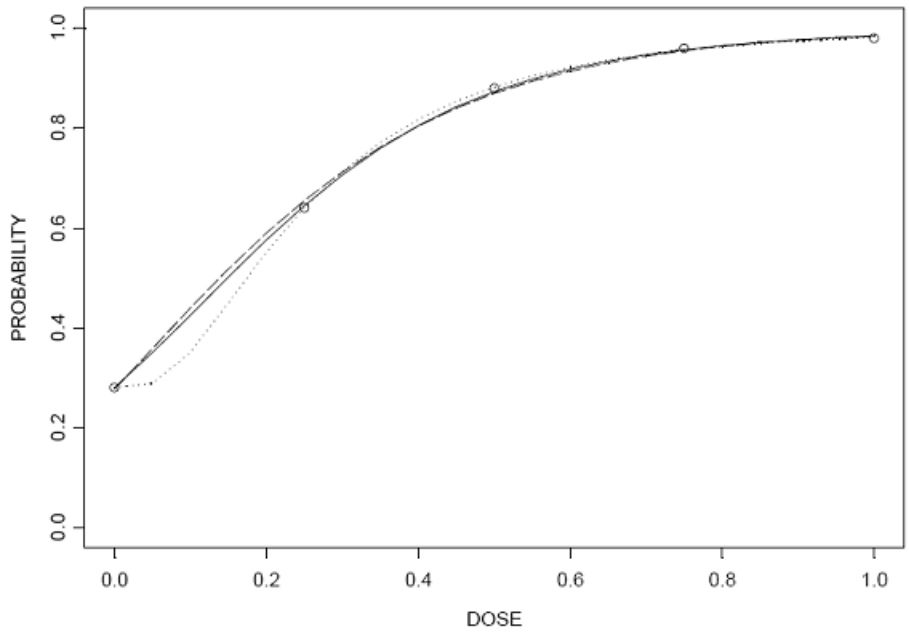


Figure 4.—Log-probit model with background dose term fitted to data.

The *log-logistic* model P = 1/(-α -β *(log(dose + η)), with parameters η = 1.5, α = -5, β = 10, was used to generate probabilities for doses 0, 0.25, 0.5, 0.75, and 1.0. Expected numbers out of 50 animals were rounded to the nearest integer, giving numbers affected of 14, 32, 44, 48, and 49. The log-probit model with background dose was fitted to these artificial data, yielding estimated parameters η = 0.567585, a = 0.946006, and b = 2.71885. The solid line shows the log-logistic model which generated the data. The dashed line shows the estimated log-probit model with background dose. The dotted line shows the estimated log-probit model with background response. Circles show the data as observed proportions of 50 animals affected. Both log-probit models fit well (Chi-square goodness of fit statistic 0.21 and 0.03, resp.); they estimated BMDs of 0.044 and 0.10, and BMDLs of 0.025 and 0.047, resp.

Application

The primary reason to apply and compare models differing in the background parameter is to better appraise model uncertainty and its implications, including uncertainty about low-dose linearity. Also, for users interested in the maximum likelihood estimate of a response at low doses and its confidence limits, it will be informative to compare these two types of models. Models with and without low-dose linearity can differ greatly in the relative risk predicted at low doses (Krewski and van Ryzin, 1981; NRC, 1980).

Some of the models with a background dose parameter may not fit data well, or may have trouble converging on a solution for the BMD or BMDL, when the observed response at zero dose is large (e.g., 20% to 50% of subjects or more)

and the dose-response pattern is unusual (either “flat” or non-monotonic at two or more doses). In other cases, especially when the control response probability is low, the two forms of model may fit a dataset almost equally well. In general, then, users are advised always to review the AIC and goodness-of-fit statistics (including the goodness-of-fit residuals) and to examine plots of the fitted model and data, before deciding whether any model, including a background dose model, fits the data adequately.

Model Fitting and Model Selection Issues

Some of the models with background dose parameter (gamma, Weibull, and log-probit models) may fail to converge on a BMDL solution in one of two situations: (1) when the response data are not strictly increasing, and (2) when the response at zero dose is positive (especially when it is large, e.g., over 20%).

When the response is not strictly increasing, most or all models may not fit well, and the following questions need to be considered:

- Is the response lower at a high dose because a competing risk is removing animals before the response can occur? If so, should responses be adjusted to account for this?[6]
- Is it reasonable to remove the high-dose group and fit a model to the reduced dataset?
- Is the response inherently non-monotonic, requiring a different type of model?

Advice on these questions is provided in the Benchmark Dose Technical Guidance document (on EPA's website: http://www.epa.gov/risk/benchmark-dose-technical-guidance).

When the response at zero dose is zero or very small, the models with background dose parameter are expected to produce a BMDL. Most cancers in rodent bioassays have zero or very low incidence in the control group.[7] With such data, models with a background dose parameter provide a useful alternative to those background-response models (i.e., the log-probit, loglogistic, gamma and Weibull quantal models) that can have extreme slopes (zero or

6 Piegorsch, W.W. and A.J. Bailer (1997) Statistics for Environmental Biology and Toxicology, London: Chapman & Hall. Gart, J.J., K.C. Chu and R.E. Tarone (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity, J. Natl. Cancer Inst. 62: 957–974. Portier, C.J. and A.J. Bailer (1989) Testing for increased carcinogenicity using a survival-adjusted quantal response test, Fund. Appl. Toxicol. 12: 731–737. Bailer, A.J. and C.J. Portier (1988) An illustration of dangers of ignoring survival differences in carcinogenic data, J. Appl. Toxicol. 8: 185–189. Kodell, R.L., D.W. Gaylor and J.J. Chen (1986) Standardized tumor rates for chronic bioassays, Biometrics 42: 867–873.

7 Portier, C.J., J.C. Hedges and D.G. Hoel (1986) Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments, Cancer Research. 46: 4372–4378. Gaylor, D.W. (1992) Relationship between the shape of dose-response curves and background tumor rates. Reg. Toxicol. Pharmacol. 16: 2–9.

infinite) as dose nears zero. However, when the response at zero dose is large, BMDL solutions may fail for some background dose models and parameter standard errors may be unusually large. These are signs of problems with near-non-identifiability of parameters and/or a very 'flat' and difficult-to solve likelihood.[8] These should be taken as warning signs that the model is probably not suitable and that the model estimates should not be relied upon.

A question of model selection could arise in comparing the traditional 2-parameter probit or logistic to the new, 3-parameter, background response versions of these models. That is, the chi-square goodness of fit may be enhanced merely by the addition of a parameter. Two considerations are pertinent. First, if either the chi-square value or the AIC value is substantially smaller for one model, it is to be preferred. Second, if the model versions differ only slightly in this respect, the generally accepted practice is to prefer the model with fewer parameters, but if the models predict substantially different BMDLs, it seems best to acknowledge the uncertainty about the true model and its BMDL. It is possible to fit a 2-parameter version of the new background response logistic and probit models by specifying that the intercept parameter be set to zero. However, this is appropriate only when the data are consistent with a response probability of 0.5 or greater for the control (because $F\{\alpha=0,\beta\} \geq 0.5$ for dose ≥ 0). This 2-parameter model could be compared to the traditional logistic or probit model with 2 parameters, and the new background response model with 3 parameters.

Interpretation

In some cases, similar models differing only in the type of background parameter (dose vs. response) may fit data almost equally well; even when they do not, there is no way to infer from mere curve-fitting which model is truer to reality. It is possible to invent even more models that might fit the data adequately but could suggest other interpretations.

The motivation for the background dose parameter was to represent an external dose or internal process acting additively to the applied dose. The background dose parameter may, but does not necessarily, represent a background exposure to the chemical applied in a bioassay or its metabolites (e.g., possible exposure from food, water or air in addition to the experimental exposure). It could also represent the outcome of biological processes generating natural metabolites that act by the same mechanism or that interfere with natural mechanisms which inhibit the mechanism; still more hypotheses could be adduced. Thus, the background dose parameter should not be interpreted

8 One useful (but not infallible) diagnostic is to plot a suitable transformation of the empirical probabilities (p = y/n) against the dose metric. If the pattern can be fit well by a linear function, then problems with near-nonidentifiability (Seber and Wild 1989) may be anticipated when fitting the corresponding model with background dose. Transformations: for the log-probit or log-logistic model with background dose, the probits or logits of p; for the Weibull model with background dose, log(-log(1-p)).

literally as support for a particular mechanism unless there is independent evidence to support the particular mechanistic interpretation. Nevertheless, it seems natural to evaluate the fit of background dose models when there is independent evidence about pre-existing or ongoing background exposure.

The background response parameter usually provides a close fit to the response of control animals if the overall model fit is good. As with the background dose parameter, one should beware of too literal an interpretation. The model could be interpreted literally to mean that a proportion γ of animals will have cancers of 'natural' origin at every dose and that a proportion (1-γ) F(dose; β) of animals will have cancers attributable to the carcinogen. This clearly goes beyond the data and its support would require experiments especially designed to test this interpretation.

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Hoel, D.G. 1980. Incorporation of background in dose-response models. Federation Proceedings 39(1): 73–75

Krewski, D., and J. van Ryzin. 1981. Dose response models for quantal response toxicity data. pp. 201–231 IN: Statistics and Related Topics. Proc. International Symposium on Statistics and Related Topics, Ottawa, May 5–7, 1980. Eds. M Csorgo, D.A. Dawson, J.N.K. Rao, and A.K.Md.E. Saleh Amsterdam: North-Holland

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NESTED MODEL DESCRIPTIONS

Special Considerations for Models for Nested Dichotomous Endpoints

The most common application of the models in this section will be to developmental toxicology studies of organisms that have multiple offspring per litter, as do rodents. In these study designs, pregnant females ("dams") are given one or several doses of a toxicant, and the fetuses, embryos, or term offspring ("pups") are examined for signs of abnormal development. In such studies, it is usual for the responses of pups in the same litter to be more similar to each other than to the responses of pups in different litters ("intra-litter correlation", or "litter effect"). Another way to describe the same phenomenon is that the variance among the proportion of pups affected in litters is greater than would be expected if the pups were responding completely independently of each other.

The models in this section make available two approaches to this feature of developmental toxicology studies: they use a probability model that provides for extra inter-litter variance of the proportion of pups affected (the beta-binomial probability model: see the "Likelihood Function" section below); and they incorporate a litter-specific covariate that is expected to account for at least some of the extra inter-litter variance. This latter approach was introduced by Rai and Van Ryzin (1985), who reasoned that a covariate that took into account the condition of the dam before dosing might explain much of the observed litter effect. Those authors suggested that litter size would be an appropriate covariate. For the reasoning to apply strictly, the measure of litter size should not be affected by treatment; thus, in a study in which dosing begins after implantation, the number of implantation sites would seem to be an appropriate measure. On the other hand, the number of live fetuses in the litter at term would not be an appropriate measure if there is any dose-related prenatal death or resorption (this has apparently been ignored in most of the literature).

Carr and Portier (1991), in a simulation study, warn that in situations in which there is no effect of litter size, statistical models that incorporate a litter size parameter, as do the models in BMDS, will often erroneously indicate that there is a litter size effect. Thus, the user should use litter size parameters with caution. Unfortunately, there are currently no good diagnostics for determining whether a litter size effect actually exists.

Likelihood Function

Let g represent the number of dose groups. For the ith group, there are n_i pregnant females administered dose $dose_i$. In the jth litter of the ith dose group there are s_{ij} fetuses, x_{ij} affected fetuses, and, potentially, a litter-specific covariate r_{ij} which will often be a measure of potential litter size, such as number of implantation sites, though this is not a requirement of the models. In what

follows, the dose-response model, which gives the probability that a fetus in the ***jth*** litter of the ***ith*** dose group will be affected is represented by

$$p(dose_i, r_{ij})$$

The beta-binomial distribution can be thought of as resulting from sampling in two stages. First, each litter is assigned a probability, P_{ij} from a beta distribution (beta distributions represent a two parameter family of probability distributions defined on the interval (0,1)). The parameters of the beta distribution are determined by the administered dose, the litter specific covariate r_{ij} and the degree of intra-litter correlation, v_i . Note that the intra-litter correlation parameter varies among doses. It is well known (Williams et al., 1988) that when the true intra-litter correlation differs among doses, unbiased estimates of the other parameters in a dose-response model can only be obtained if dose-specific intra-litter correlation parameters are estimated. As a special case, if v_i =0, then this part of the process is completely deterministic, and

$$P_{ij} = p(dose_i, r_{ij})$$

This allows for the possibility of no litter effect at all.

In the second stage of sampling, s_{ij} ***fetuses*** are assigned to the litter, and the number of affected fetuses, x_{ij} is sampled from a binomial distribution with parameters P_{ij} and s_{ij} .

The log-likelihood function that results from this process is:

$$\mathrm{L} = \sum_{i=1}^{g} \left\{ \sum_{j=1}^{n_i} \left[\sum_{k=1}^{x_{ij}} \ln\left(p(dose_i, r_{ij}) + (k-1)\psi_i\right) + \right.\right.$$

$$\sum_{k=1}^{s_i j - x_{ij}} \ln\left(1 - p(dose_i, r_{ij}) + (k-1)\psi_i\right) -$$

$$\left.\left. \sum_{k=1}^{s_i j} \ln(1 + (k-1)\psi_i), \right.\right.$$

where

$$\psi_i = \frac{\phi_i}{1 - \phi_i}$$

and

$$\sum_{a}^{b}(.) = 0$$

if ***a > b*** by convention.

Goodness of Fit Information—Litter Data

The "Litter Data" table provides a listing of the data, expected and observed responses and scaled residuals, for each litter.

The scaled residual values printed in the last column of the table are defined as follows:

(Obs.—Expected)/SE

where "Expected" is the predicted number of responders from the model and SE equals the estimated standard error of that predicted number. For these models, the estimated standard error is equal to sqrt[n*p*(1-p)*(*ϕ(n-1)+1)], where

- n is the sample (litter) size,
- p is the model-predicted probability of response, and
- f is the model-predicted intra-litter correlation coefficient.

The overall model should be called into question if the scaled residual values for several individual dose and litter-specific covariate combinations, particularly for a dose group near the BMD and for litter-specific covariate values close to the overall mean, are greater than 2 or less than -2.

The goodness-of-fit p-values are calculated using a bootstrap approach.

1. The MLE parameter values are used to generate B pseudo-datasets having the same design features (number of doses and number of litters per dose), litter-sizes, and, if necessary, litter-specific covariate values, as the original dataset. What varies from pseudo-dataset to pseudo-dataset are the number of responding "units" within litters, and those are generated, at random, as dictated by the values of the ML estimates.
2. Once the B bootstrap iterations are generated, a statistic referred to as *chi-square* is calculated for each. The chi-square statistic is the sum of the squares of the scaled residuals for each litter, as described above. Higher values of that statistic are indicative of poorer match between the model predictions and the data.

> ***Note*** The chi-square statistic is so called here because, in traditional testing situations, that statistic would be approximated by a chi-squared random variable have a certain degrees of freedom, and its "significance" (p-value) would be determined from the appropriate chi-squared distribution function.

3. The chi-square statistic from the original data is computed and compared to the values from the B bootstrap iterations. The p-value is the proportion of chi-square values from the iterations that are greater than the original chi-square value.

   High p-values are indicative of adequate fit (i.e., there was a high proportion of chi-square values associated with pseudo-datasets obtained from data known to be consistent with the model and the ML estimates of the model parameters).

That calculation is repeated three times, and various percentiles of the generated chi-square statistic are presented. This allows the user to determine if enough bootstrap iterations (B) have been specified. The default for B is 1000 and should probably not be reduced. The user may wish to increase the default (via the Nested Model Option Screen) if the percentiles for chi-square differ markedly across the three runs (in particular the median and lower percentiles), or if the p-values calculated from the three runs differ markedly. This may only be an issue when the p-value is close to the value (e.g., 0.05 or 0.10) used as a critical value for deciding whether or not the fit of the model to the data is adequate. If there is some variability in the p-values, but they are all greater than 0.20, for example, then one probably need not worry about increasing the value for B.

BMD Computation

BMD computation is similar to that for dichotomous models with the added wrinkle that a value for the litter-specific covariate is required. The user has the option of specifying either the control group mean of the covariate, or the overall mean. In most cases, the overall mean should be preferred, if the covariate is not expected to be affected by dose. If the covariate is affected by dose, then it should probably not be used.

BMDL Computation

BMDS currently only calculates one-sided confidence intervals, in accordance with current BMD practice. The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985).

The approach used for all the nested dichotomous models is the same. The equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters, using

either the control group mean or the overall mean of the litter-specific covariate. The resulting expression is substituted back into the model equations, with the effect of re-parameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{x^2_{1,1-2\alpha}}{2}$$

See also:

- Nested Models Option Screens
- Nested Model Options Fields
- Nested Models—Text Output
- Logistic Nested Model Description
- NCTR Model Description
- Rai and Van Ryzin Model Description
- Optimization Algorithms Used In BMDS

LOGISTIC NESTED MODEL

Model Form

The Nested Logistic Model is the log-logistic model, modified to include a litter-specific covariate. The model form for the Nested Logistic Model is:

$$\text{Prob}\{response\} = \frac{\alpha + \theta_1 r_{ij} + \left(1 - \alpha - \theta_1 r_{ij}\right)}{\left(1 + \exp\left[-\beta - \theta_2 r_{ij} - \rho * \ln(dose)\right]\right)}$$

if *dose* > 0, and $\alpha + \theta_1 r_{ij}$ if *dose* = 0.

In the above equation, r_{ij} is the litter-specific covariate for the *jth* litter in the *ith* dose group; $\alpha \geq 0$, $\beta \geq 0$, $\rho \geq 0$ with an option to restrict $\rho \geq 1$; and $1 > \alpha + \theta_1 r_{ij} \geq 0$ for every r_{ij} .

In addition there are g intra-litter correlation coefficients, $\mathbf{0} \leq \phi_i \leq \mathbf{1}$ (i = 1, …, g).

Parameters

- Intercept = α

- Power = ρ
- Slope = β
- First coefficient for litter-specific covariate = θ_1
- Second coefficient for liter-specific covariate = θ_2
- Intralitter correlation coefficients = $\phi_1 \ldots \phi_g$ (If ϕ is specified or initialized, ϕ must be a number > 0 and < 1.)

Special Options

- **Restriction**: Power parameter ρ **(rho)** can be restricted to be ≥ 1 (Default)

Risk Type

Choices are "Extra" or "Added." Additional risk is the additional expected proportion of total animals that respond in the presence of the dose, or the mean probability of response at dose d, P(d), minus the mean probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the expected proportion of animals that will not respond in the absence of exposure, 1—P(0). Thus, extra and additional risk are equal when the expected background rate is zero.

BMD Computation

If r_m represents either the control mean value for the litter-specific covariate or its overall mean, then the BMD is computed as:

$$BMD = \exp\left\{\frac{\ln\left(\frac{A}{1-A}\right) - \beta - \theta_2 r_m}{\rho}\right\}$$

where

A = BMRF for extra risk

= BMRF/(1—a—$\theta_1 r_m$) for added risk

BMDL Computation

The parameter β is replaced with an expression derived from the BMD definition (above) in the dose-response function, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{x^2_{1,1-2\alpha}}{2}$$

See also:

- Nested Model Descriptions
- Nested Model Options Fields
- Nested Logistic Model Input File

NCTR MODEL

Model Form

The NCTR model is a Weibull model modified to include a litter-specific covariate. The model form is:

$$\text{Prob}\{response\} = 1 - \exp\left\{-\left(\alpha + \theta_1(r_{ij} - r_m)\right) - \left(\beta + \theta_2(r_{ij} - r_m)\right) dose^{\rho}\right\}$$

where ***rij*** is the litter-specific covariate for the ***jth*** litter in the ***ith*** dose group, r_m is the overall mean for the litter-specific covariate, $\alpha \geq 0$, $\beta \geq 0$, $\rho \geq 0$ with an option to restrict $\rho \geq 1$, and

$$\theta_1(r_{ij} - r_m) \geq 0 \text{ and } \theta_2(r_{ij} - r_m) \geq 0$$

for every ***rij***.

In addition there are g intra-litter correlation coefficients, $0 \leq \phi_i \leq 1$ (i = 1,…, g).

Parameters

- Intercept = α
- Power = ρ
- Slope = β
- First coefficient for litter-specific covariate = θ_1
- Second coefficient for liter-specific covariate = θ_2
- Intralitter correlation coefficients = ϕ_1 …ϕ_g (If ϕ is specified or initialized, ϕ must be a number > 0 and < 1.)

Special Options

- **Restriction:** Power parameter ρ **(rho)** can be restricted to be $\geq$ 1 (Default)

Risk Type

Choices are “Extra” or “Added.” Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure,

P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1—P(0). Thus, extra and additional risk are equal when background rate is zero.

BMD Computation

$$BMD = \left[-\frac{\ln(1-A)}{\beta + \theta_2 \delta_r}\right]\left(\frac{1}{\rho}\right)$$

where δ_r is the average of (r_{ij}—r_m) over either the control group or over all observations, depending upon the option selected for "Fixed Litter Size" (when using the overall mean, δ_r is always 0), and

A = BMRF for extra risk

= BMRF/(1-α- θ_1 δ_r) for added risk

BMDL Computation

The parameter β is replaced with an expression derived from the BMD definition (above) in the dose-response function, with the effect of reparametrizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{x^2_{1,1-2\alpha}}{2}$$

See also:

- Nested Model Descriptions
- NCTR Model Input File Format

RAI AND VAN RYZIN MODEL

Model Form

The Rai and Van Ryzin model is a Weibull model modified to include a litter-specific covariate. The model form is:

$$\text{Prob}\{response\} = [1 - \exp\{-\alpha - \beta \cdot \text{dose}^{\rho}\}] \cdot \exp\{-(\theta_1 + \theta_2 \text{dose}) \cdot r_{ij}\}$$

where ***r_{ij}*** is the litter-specific covariate for the ***jth*** litter in the ***ith*** dose group, $\alpha \geq$ **0**, $\beta \geq$ **0**, $\theta \geq$ **0** with an option to restrict $\theta \geq$ **1**, and

$\theta_1 + \theta_2 dose_j > 0$, for all doses (i = 1, …, g).

In addition there are g intra-litter correlation coefficients, **$0 < \phi_i < 1$** (i = 1, …, g)**.**

This is a generalization of the model described in Rai and Van Ryzin (1985) by the addition of the power parameter, ρ. To get the conventional Rai and Van Ryzin model, fix the power parameter to 1.

Parameters

- Intercept = α
- Power = ρ
- Slope = β
- First coefficient of litter-specific covariate = θ_1
- Second coefficient of litter-specific covariate =θ_2
- Intralitter correlation coefficients = ϕ_1 …ϕ_g (If ϕ is specified or initialized, ϕ must be a number > 0 and < 1.)

Special Options

- **Restriction**: Power parameter ρ **(rho)** can be restricted to be $\geq$ 1 (Default)

Risk Type

Choices are “Extra” or “Added.” Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1—P(0). Thus, extra and additional risk are equal when background rate is zero.

BMD Computation

The BMR formulas are solved numerically for the BMD.

BMDL Computation

The parameter β is replaced with an expression derived from the BMD definition in the dose-response function, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\frac{x^2_{1,1-2\alpha}}{2}$$

See also:

- Nested Model Descriptions
- Ray and Van Ryzin Model Input File

REPEATED RESPONSE MEASURES MODEL DESCRIPTION

Model Form

The Repeated Response Measures model has the following form for describing the time course of responses before and after an exposure to a dose:

$$\eta(d,t) = \frac{A(t) + B \cdot t \cdot d \cdot \exp(-k \cdot t)}{(1 + C \cdot d \cdot t \cdot \exp(-k \cdot t))}$$

where

A(t) = A0 ,or

A(t) = A0 + A1 t ,or

A(t) = A0—A1 t + A2 t2

depending on the “background degree” specified by the user. A(t) applies before exposure and for all times in the absence of exposure (or to “sham” exposures to dose=0). Thus the Repeated Response Measures model is applicable to data with the following characteristics:

- An outcome (response variable) measured on a continuous scale.
- Single exposure (or exposure interval), to several (4–5 recommended) “dose” levels.
- Duration of the experiment (the time component) coded between 0 and a maximum positive value, with 0 being the beginning and the maximum positive value the last time point at which data are available. The time at which exposure took place must be known and coded by a value between 0 and the maximum value.
- The outcome is observed (and recorded) repeatedly over time on each study subject; the timing of the observation is given. It is not required, however, that each subject (experimental unit) yield an equal number of observations at the same time points.
- Observations should not be aggregated over subject, and data must be identifiable with each subject.
- Multiple subjects per dose group.

- Dose effects are preferably observed at more than one dose level.
- Differences in dose effects are seen at some time points.

The model fitting is accomplished by maximizing the likelihood of the data, assuming a random effects model for the parameter A_0 (normally distributed across individuals) and a normal error distribution (observations are normally distributed around the model-predicted individual-, dose-, and time-specific means).

Parameters

- Background parameters = A_0 , A_1 , A_2
- Time-course parameters = B, C, k

Special Options

- None

Risk Type

Risk is defined in terms of added or extra risk. Because the Repeated Response Measures model is for continuous responses, this requires specification of response levels that are considered adverse. That is done in one of two ways. First, the assumed background rate (probability) of adverse response may be specified; in that case the cut-off(s) that yield that probability of response are determined from the fit of the model. Second, the cut-off value(s) may be specified directly; that yields an estimated background rate of response once the model is fit. In either case, the extra or added risk is calculated for any dose (and time) based on the model-predicted increase in the proportion of responses beyond the cut-off(s).

BMD Computation

The BMD output from a Repeated Response Measures model run is the lowest dose for which, at some time after exposure, the extra or added risk is equal to the BMR Risk Level specified by the user. Note that because the response rates vary over time, there will be several dose levels that yield the BMR response at various time points. The minimum of those doses is the reported minimum BMD.

BMDL Computation

The BMDL is estimated via bootstrap resampling of residuals and random effects. The residuals and random effects are estimated from the original fitting of the model. They are resampled (within or across dose groups) treating the vector of residuals for an individual as the sampling unit if need be. BMDs are calculated as discussed above for each set of bootstrapped observations. The percentiles over all the bootstrapped BMDs are used to define confidence bounds for the BMD (e.g., the 5th percentile would be reported as the 95% lower bound on the BMD).

References

For more information, see Zhu, Y., Jia, Z., Wang, W., Gift, J., Moser, V.C., and B.J. Pierre-Louis (2005), "Data Analysis of Neurobehavioral Screening Data: Benchmark Dose Estimation." *Regulatory Toxicology and Pharmacology*, pp 190–201.

See also:

Repeated Response Measures

CONCENTRATION X TIME MODEL DESCRIPTION

Model Form

There is only one Concentration x Time model currently in BMDS, which has the following form:

$$\text{Prob}\{response\} = h(z)$$

where h() is either the logit or the probit function

$h(z) = \frac{\exp(z)}{(1+\exp(z))}$ for Logit link function

$h(z) = \varphi(z - 5)$ for Probit link function.

and φ() is the standard normal cumulative distribution function. The variable z is a linear function of the terms in the model as follows:

$$z = B_0 + B_1 * f_C(C) + B_2 * f_T(T) + B_3 * f_x(x) + B_4 * r_4(C,T,x) + B_5 * r_5(C,T,x) + \cdots$$

where

f_i (u) = transformation of concentration (i=C), time (i=T), or covariate (i=x);

r_j (C, T, x) = interactions (products) of the f_C (C), f_T (T), and f_X (x) terms.

The f_i transformations that have been implemented are described in .

Table 29: *$f_i(u)$ transformations implemented in BMDS*

$f_i(u)$ =	Transformation
u	Identity
ln(u)	Logarithmic
1/u	Reciprocal

Note that the covariable “x” is actually a place holder for any number of possible explanatory variables of interest (think of x as a vector of variables above and beyond the C and T variables).

Parameters

- Intercept = B_0
- Coefficients of the model terms = B_1 , …, B_n

Currently the BMDS version of the model allows up to five main effects variables and three product terms, so that $n \leq 8$.

Special Options

None

Risk Type

There are no specific risk type choices. The model calculates a concentration (or the value of any other variable) given the values of the other variables in the model such that the *probability* of response is equal to some specified value. If the background probability is 0, as it would be if the logarithmic transformation is used for all the explanatory variables in the model, then the probability of response for a set of values for the model variables is equal to the added or extra risk for that set of values.

BMD Computation

The BMD (concentration yielding a specific probability of response, given the values of the other model variables) is computed numerically from the set of MLE parameter values.

BMDL Computation

A Wald-type confidence interval is determined for all model parameters (including the “BMD” as defined above). The confidence bounds determined in this manner for the BMD yield the BMDL (and a BMDU, an upper bound on the BMD). The user must specify a deviate value corresponding to the confidence level of interest; this deviate can be determined from the standard normal distribution or, perhaps more appropriately, from a T distribution with degrees of freedom determined from the number of observations and the number of fitted parameters.

Graphics

Note about model graphics: because the graphical representation of the Concentration x Time modeling results is quite different from that obtained from other BMDS models, the current version of BMDS does not include a direct graphical output for the Concentration x Time model. However, an Excel

spreadsheet tool is available that allows users desiring graphical outputs to create plots of:

- Contours of response probabilities on the Concentration-Time plane: the contour for a chosen probability of response shows the curve for the combinations of concentration and time that yield the chosen probability or response (conditional on the values of other covariates in the model, set by the user).
- The probability of response (y-axis) as a function of either concentration or time (x-axis), fixing the other variable (and the other covariates in the model) at values of the user's choice.

See Also:

- Concentration x Time Model Option Screen
- Concentration x Time Data

MULTITUMOR (MS_COMBO) MODEL DESCRIPTION

The purpose of the MS_Combo program in BMDS is to allow the user to calculate BMDs and BMDLs for a combination of tumors (corresponding to a defined risk of getting one or more of those tumors) when the individual tumor dose-responses have been modeled using a Multistage-Cancer model.

Thus, the output of an MS_Combo run will present the results of fitting each individual tumor (including the BMD and BMDL for that tumor) plus the combined log-likelihood, BMD and BMDL for the combination of specified tumor responses.

In practice, the user should investigate each tumor individually and determine which degree of the Multistage-Cancer model is most appropriate for each individual tumor. That determination will involve all the usual considerations of fit, AIC, etc.

Once a specific form of the Multistage-Cancer model is chosen for each of the tumors of interest (they need not have the same degree across all of the tumors in question), the user should specify those choices in the MS_Combo run.

Note The following descriptions are valid only when the tumors are assumed to be independent of one another (conditional on dose level).

Because of the form of the multistage model, the MLE estimates for the combined risk are a function of the parameter values obtained for the individual

tumor multistage model fits. In fact, the combined probability function has a multistage model form:

$$P(d) = 1 - \exp\{-(\beta_0 + \beta_1 d + \beta_2 d_2 + \cdots)\}$$

and the terms of the combined probability function (β_0, β_1, …) are specified as follows

$$\beta_0 = \sum \beta_{0i}$$

$$\beta_1 = \sum \beta_{1i}$$

$$\beta_2 = \sum \beta_{2i}$$

etc.

where the sums are over i = 1, …, t, with

- t being the number of tumors under consideration, and
- β_{xj} being the x^{th} parameter (0, 1, …) for tumor j.

The β_{xj} values are available directly from the Multistage-Cancer runs performed on the individual tumors, but MS_Combo performs the calculations for the user, completing the summations of the individual terms and computing the BMD based on the combined parameter values and the user-specified BMR.

A profile-likelihood approach is used to derive the BMDL.

- Given the BMD and the log-likelihood associated with the MLE solution, a target likelihood is defined based on the user-specified confidence level (e.g., 95%).
- That target likelihood is derived by computing the percentile of a chi-square (1 degree of freedom) corresponding to the confidence level specified by the user (actually, the alpha associated with the confidence level, times 2).
- That percentile is divided by 2 and subtracted from the maximum log-likelihood.
- That derivation is based on a likelihood ratio test with one degree of freedom; it can be shown that estimating the BMDL corresponds to losing one degree of freedom, regardless of the number of tumors being combined.

The BMDL for the combined response (one or more of the tumors of interest) is defined as the smallest dose, D, for which the following two conditions are satisfied:

- There is a set of parameters such that the combined log-likelihood using D and those parameters is greater than or equal to the target likelihood), and
- For that set of parameters, the risk at D is equal to the user-specified BMR.

Note that the combined log-likelihood is a function of the fits of the individual tumors (the sum of the individual log-likelihoods), obtained using their tumor-specific β values. Thus, the search for the parameters of the combined Multistage-Cancer model varies the individual-tumor β values in such a way that the individual log-likelihoods add up to a combined likelihood within the range desired (greater than or equal to the target). However, in order to satisfy the second constraint, the sums of the individual-tumor parameters (shown above to be the parameters of the combined probability function) are used to evaluate the risk for any proposed BMDL, D.

Note that the individual tumors need not be modeled with the same degree of the Multistage-Cancer model. Any terms not included for an individual tumor are assumed to be zero (and will remain at zero during BMDL optimization) in the summations shown above. The optimizer DONLP2 is used for the combined BMDL estimation.

See also:

- Multistage and Multistage-Cancer Model
- MS_Combo Model Input File
- Optimization Algorithms Used in BMDS

APPENDIX A: INPUT FILE FORMAT DESCRIPTIONS

Note All file formats are now created using data entry screens and options screens,

The input file formats described in this section reflect earlier versions of BMDS (and its precursors) for which the users had to enter data and model options directly into the input file. As a result, the information in this section should be considered as historical reference and not required for use with current versions of BMDS (versions 2.2 and higher).

Input file formats for the Repeated Response Measures and Concentration x Time models (which were not included in earlier versions of BMDS) are not described here. The Repeated Response Measures and Concentration x Time models cannot be run outside of the current BMDS GUI. For more information on creating datasets and modeling options for these models, refer to the model description (Repeated Response Measures Model Description, Concentration x Time Model Description) and option screen sections (Repeated Response Measures Option Screen, Concentration x Time Model Option Screen) of this documentation.

Descriptions of Dichotomous Model Data Input Text Files

- Gamma-hit Model Input File Format
- Logistic and Log-Logistic Models Input File Format
- Multistage (Polynomial) Model Input File Format
- Probit and Log-Probit Models Input File Format
- Quantal Linear Model Input File Format
- Weibull Model Input File Format

Descriptions of Dichotomous Alternative Model Data Input Text Files

- Dichotomous Alternative Hill Model Input File
- Weibull Dichotomous Alternative Model with Background Dose Input File

Descriptions of Continuous Model Data Input Text Files

- Linear Model Input File Format
- Polynomial Model Input File Format
- Power Model Input File Format
- Hill Model Input File Format
- Exponential Continuous Models Input File Format

Descriptions of Nested Model Data Input Text Files

- Logistic Model Input File Format
- NCTR Model Input File Format
- Rai and Van Ryzin Model Input File Format

Description of Multiple Tumor Model Data Input Text Files

- MS_Combo Model Input File

Each model listed above is a separate executable file that makes use of DOS text input files. The DOS text files provide the "instructions" for the model run. The BMDS interface software assists users in the creation of properly formatted input files for the model executables. The text file format for these data input files are model specific and can be obtained by following the above links. Each model can be run from the DOS command line of your computer by typing the model file name followed by the complete name (including directory location and extension) of an associate data input file (BMDS expects these files to be labeled with a .(d) extension, but the model executables will accept any extension).

The model will generate both a text output (.out) and a graphic (.002) file with the same name prefix as the .(d) file. The .out file can be read with any text editor. The BMDS interface automatically creates a plot (.plt) file from the .002 file and displays it using the GNUPlot program you should have installed with BMDS. Plot files can also be created from the DOS command line of your computer by typing the name of the scripter file associated with the continuous (00*.exe), nested (05*.exe) or dichotomous (10*.exe) model that was used, followed by the complete name (including directory location and extension) of the .002 file associated with the model run. The wgnupl32.exe program included with the BMDS installation can then be used to view or edit the plot (.plt) file.

BMDS operates in a Windows environment and automatically performs the DOS process commands when a session is run.

CANCER DICHOTOMOUS MODEL INPUT FILE

[1] Model name, in this case, the string Multistage-Cancer

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6] Degree of Polynomial

[7a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[7b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[7c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[8] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[9] Restrict Betas >= 0

= 1 if Restrict Betas >= 0 box is checked

= 0 otherwise

Note In the cancer model, this parameter will always be set equal to 1.

[10] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

Note This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Beta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18+] Etc. for Beta3, Beta4 . . .

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[20] Background Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Beta1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Beta2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22+] Etc. for Beta3, Beta4, …as necessary

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Multistage
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6] 2
[7-12]250 2.22045e-16 1.49012e-8 1 1 0 1 1
[13-15] 0.10 0 0.95
[16-18+]-9999 -9999 -9999
[19] 0
[20-22+]-9999 -9999 -9999
[23-25]Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

DICHOTOMOUS ALTERNATIVE HILL MODEL INPUT FILE

[1] Model name, in this case, the string Dichotomous-Hill

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[11] Smooth Option

= 0 if Unique

= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra

= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] v Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] g Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Intercept Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[20] v Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] g Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Intercept Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Dose Name

[25] Response Name

[26] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Dichotomous-Hill
[2] BMDS MODEL RUN
[3] C:\usepa\BMDS260\Data\Dichotomous.dax
[4] C:\usepa\BMDS260\Data\dhl_Dichotomous_Opt.out
[5] 5
[6-11]500 1.00E-08 1.00E-08 0 1 1 0 0
[12-14]0.1000 0 0.95
[15-18]-9999 -9999 -9999 -9999
[19] 0
[20-23]-9999 -9999 -9999 -9999
[24-26] Dose Percent NEGATIVE_RESPONSE
0 2.34 97.66
50 4.58 95.42
100 42.5 57.5
150 60 40
200 90.23 9.77
```

See also:

Input File Format Descriptions

Dichotomous Hill Model

GAMMA DICHOTOMOUS MODEL INPUT FILE

[1] Model name, in this case, the string Gamma

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[11] Smooth Option

= 0 if Unique

= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra

= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[19] Background Parameter.

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[20] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Power Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Gamma
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6-11] 250 2.22045e-16 1.49012e-8 1 1 1 1 0
[12-14] 0.10 0 0.95
[15-17] -9999 -9999 -9999
[18] 0
[19-21] -9999 -9999 -9999
[22-24] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

Gamma-hit Model Description

EXPONENTIAL CONTINUOUS MODEL INPUT FILE

[1] Model Name, in this case, the constant string Exponential

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 0 if individual animal data (e.g., Dose, Response) are entered

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)

[6] A count of the number of observations

[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)

= 1 if Up (dose-response curve trends up with increasing dose)

= -1 if Down (dose-response curve trends down with increasing dose)

[8] Run Models

One digit per model indicating whether it is included in the run. For example, “1000” runs only Model 2 and “1111” runs Models 2, 3, 4, and 5.

= 0 if No

= 1 if Yes

[9] Span

Two digits indicating first and last model to run. For example, “11” means that Model 2 is first and last; “14” means that Model 2 is first and Model 5 is last.

[10] Distribution Curve

= 0 is Normal

= 1 is Lognormal

[11] Maximum Likelihood Estimate (MLE) Solution

= 0 is Approximate

= 1 is Exact

> ***Note*** If Distribution Curve is 0, then MLE Solution should always be 1 (Exact). If Distribution Curve is 1 and Input Type (line 5) is 1, then MLE Solution should always be 0 (Approximate).

[12] Maximum # of iterations

= 500

[13] Rel Function Convergence

= -1.00e-8

[14] Parameter Convergence.

= -1.00e-8

[15] BMDL Curve Calculation

= 0 (BMDL Curve Calculation box is unchecked)

[16] BMD Calculation

= 1 (BMD calculation box is checked)

[17] Append or Overwrite Output File

= 0 if Overwrite is selected

= 1 if Append is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[18] Smooth Option

= 0 (Unique)

[19] BMR Type

= 0 if Absolute Dev.

= 1 if Std. Dev.

= 2 if Relative Dev.

= 3 if Point

[20] BMRF (BMR Level)

= User input value (or default of 1.000)

[21] Constant Variance

= 0 if not checked (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)

= 1 if box is checked (rho is set to 0 in the above equation)

[22] Confidence Level

= User input value (or default of .950)

[23] Alpha Parameter

= -9999

[24] Rho Parameter

= -9999

[25] a Parameter

= -9999

[26] b Parameter

= -9999

[27] c Parameter

= -9999

[28] d Parameter

= -9999

[29] Initialize Parameters

= 0

[etc.]

> ***Note*** In the Exponential software, no initial values may be specified by the user. Leave all these entries as is (with "-9999").

[30]-[33] In this order, by checking the column assignment pull down menus, these fields should contain:

If Group data are entered:

[30] Dose header

[31] N header

[32] Mean header

[33] Std header

If Individual data are entered:

[30] Dose header

[31] Response header

[etc.]

In the same column order as above, this should just be a data listing.

Format Example

```
[1] Exponential
[2] Default settings but downward adversity
[3] C:\software\EPA\BMDS250\Data\Continuous1.dax
[4] C:\software\EPA\BMDS250\Data\exp_Continuous1_exptest.out
[5-11] 1 5 -1 1111 14 0 1
[12-18] 500 1.00E-08 1.00E-08 0 1 1 0
[19-22] 1 1.00 1 0.95
[23-28] -9999 -9999 -9999 -9999 -9999 -9999
[29] 0
```

```
[23-28] -9999 -9999 -9999 -9999 -9999 -9999
[23-28] -9999 -9999 -9999 -9999 -9999 -9999
[29] 0
[23-28] -9999 -9999 -9999 -9999 -9999 -9999
[23-28] -9999 -9999 -9999 -9999 -9999 -9999
[29] 0
[23-28]-9999 -9999 -9999 -9999 -9999 -9999
[23-28]-9999 -9999 -9999 -9999 -9999 -9999
[29] 0
[23-28]-9999 -9999 -9999 -9999 -9999 -9999
[30-33] DOSE N MEAN STD
0 20 6 1.2
25 20 5.2 1.1
50 19 2.4 0.81
100 20 1.1 0.74
200 20 0.75 0.66
```

See also:

Input File Format Descriptions

Exponential Models Description

Unique Options for Exponential Models

Continuous Exponential Model Options Fields

HILL CONTINUOUS MODEL INPUT FILE

[1] Model Name, in this case, the constant string Hill

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)

= 0 if individual animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)

= 1 if Up (dose-response curve trends up with increasing dose)

= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[9] BMDL Curve Calculation

= 0 (BMDL Curve Calculation box is unchecked)

[10] Restrict n > 1?

= 1 if Restrict n > 1 box is checked

= 0 otherwise

[11] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[13] Smooth Option

= 0 if Unique

= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.

= 1 if Std. Dev.

= 2 if Relative Dev.(Default)

= 3 if Point

= 4 if Extra

[15] BMR (BMR Level)

= User input value (Default = 0.1000)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)

= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Intercept Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] v Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] n Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] k Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[25] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[26] Rho Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[27] Intercept Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[28] v Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29] n Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[30] k Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[31]-[34]

IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:

If Group data is entered:

[31]	[32]	[33]	[34]
Dose name	N name	Mean Name	Std Name

If Individual data is entered:

[31]	[32]
Dose name	Response name etc.

In the same column order as above, this should just be a data listing.

Example Format

```
[1] Hill
[2] BMDS MODEL RUN
[3] HYBRID1.SET
[4] HYBRID1
[5-7] 1 6 1
[8-13] 250 2.22045e-16 1.49012e-8 1 0 1 1 1
[14-17] 1 1.00 1 095
[18-23] -9999 -9999 -9999 -9999 -9999 -9999
[24] 0
[25-30] -9999 -9999 -9999 -9999 -9999 -9999
[31-34] DOSE NI MEAN STD
0 4 38.45 1.1683
8 5 39.56 1.28218
20 4 40.9 1.303
30 4 41.95 1.418203
40 4 42.725 1.438
50 5 43.42 1.45932
```

See also:

Input File Format Descriptions

Hill Model Description

LINEAR CONTINUOUS MODEL INPUT FILE

Use Polynomial Continuous Model Input File Format, but make sure the polynomial degree (Item 4a) is set to 1.

LOGISTIC AND LOG-LOGISTIC DICHOTOMOUS MODEL INPUT FILES

[1] Model name, in this case, the string Logist

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Log Transformation

= 1 if Log transformation is to be used

= 0 otherwise

[9] Restrict Slope >= 1

= 1 if Restrict Slope >= 1 box is checked (only appropriate for log-logistic model)

= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value or if Log transformation not selected

[17] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Intercept Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[20] Background Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected or if Log transformation not selected

[21] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Intercept Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Logist
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6-12] 250 2.22045e-16 1.49012e-8 1 0 0 1 1 0
[13-15] 0.10 0 0.95
[16-18] -9999 -9999 -9999
[19] 0
[20-22] -9999 -9999 -9999
[23-25] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

LOGISTIC NESTED MODEL INPUT FILE

[1] Model name, in this case, the string Nlogist

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Fixed Size

= 1 if Ctrl Group Mean selected

= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Bootstrap Iterations

= User input value (or default of 1000)

[17] Seed

= If specified, user input value in decimal format (or default of 0)

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Beta Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Theta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Theta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Phi3 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[26+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[27] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[28] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29] Rho Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[30] Beta Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[31] Theta1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[32] Theta2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[33] Phi1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[34] Phi2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[35] Phi3 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[36+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[37] Dose Name

[38] Response Name

[39] Constant String: NEGATIVE_RESPONSE

[40] Litter Size

[41] Column 5 name

Data

Dose in first column

Response in Second

Total (Litter Size) minus Response in third column

Litter Specific Covariate

Group number, or any integers

Example Format

```
[1] Nlogistic
[2] BMDS MODEL RUN
[3] C:\usepa\BMDS260\Data\Nested.dax
[4] C:\usepa\BMDS260\Data\nln_Nested_Opt.out
[5-5a] 39 4
[6-12] 500 1.00E-08 1.00E-08 1 0 1 1 0 0
[13-17] 0.1000 0 0.95 1000 0
[18-22] -9999 -9999 -9999 -9999 -9999
[23-26+] -9999 -9999 -9999 -9999
[27] 0
[28-32] -9999 -9999 -9999 -9999 -9999
[33-36+] -9999 -9999 -9999 -9999
[37-41] Dose Resp Negative_Response Covariate Column 5
```

```
0 1 15 16 -9999
0 1 8 9 -9999
0 2 13 15 -9999
0 3 11 14 -9999
0 3 10 13 -9999
0 0 9 9 -9999
0 2 8 10 -9999
0 2 12 14 -9999
0 1 9 10 -9999
0 2 9 11 -9999
25 4 10 14 -9999
25 5 4 9 -9999
25 6 8 14 -9999
25 2 7 9 -9999
25 6 7 13 -9999
25 3 9 12 -9999
25 1 9 10 -9999
25 2 8 10 -9999
25 4 7 11 -9999
25 3 11 14 -9999
50 4 7 11 -9999
50 5 6 11 -9999
50 5 9 14 -9999
50 4 7 11 -9999
50 5 5 10 -9999
50 4 7 11 -9999
50 5 5 10 -9999
50 6 9 15 -9999
50 2 5 7 -9999
50 4 10 14 -9999
100 6 5 11 -9999
100 6 8 14 -9999
100 8 4 12 -9999
```

```
100 7 6 13 -9999
100 8 4 12 -9999
100 6 8 14 -9999
100 6 5 11 -9999
100 5 3 8 -9999
100 4 6 10 -9999
```

See also:

Input File Format Description

Logistic Nested Model Description

MS_COMBO MODEL INPUT FILE

[1] Model name, in this case, the string MS_Combo

[2] User notes

[3] Data file name (.dax) including path of first tumor (file names appear in output)

[4] Number of tumors for combined BMDL. The number entered here determines the additional lines required following Line 11.

[5–11] Info for first tumor

[5] X Y Z where X=# dose groups, Y=degree of polynomial, Z=Input dax file name (sans path)

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[6d] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[6e] Restrict Power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[6f] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[6g] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[6h] Smooth Option

= 0 if Unique

= 1 if C-Spline

[7a] BMR (BMR level)

= User input value (or default of .100)

[7b] Risk Type

= 0 if Extra

= 1 if Added

[7c] Confidence Level

= User input value (or default of .950)

[8] Specified parameters (or default values); count = Y + 1 where Y is from line 5

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[9] Number of initialized parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[10] Initialized parameters (or default values); count = Y + 1

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[11] Header names for experimental data

[12ff—line count depends on value from Line 5] Data

[Repeat lines 5–12ff for each dax file]

Note This format can be extended for up to 10 tumor files.

Example Format

The following example shows three .dax files represented in the MS_Combo model input file.

```
[1] MS_Combo
[2] BMDS_Model_Run
[3] C:\USEPA\BMDS240\Data\Dichotomous.dax
[4] 3
[5] 5 2 Dichotomous.dax
[6a-6h] 500 1.00E-08 1.00E-08 0 1 1 0 0
[7a-7c] 0.01 0 0.95
[8] -9999 -9999 -9999
[9] 0
[10] -9999 -9999 -9999
[11] Dose Effect NEGATIVE_RESPONSE
[12+] 0 0 100
 50 5 95
 100 30 70
 150 65 35
 200 90 10

[5] 5 2 Dichotomous.dax
[6a-6h] 500 1.00E-08 1.00E-08 0 1 1 0 0
[7a-7c] 0.01 0 0.95
[8] -9999 -9999 -9999
[9] 0
[10] -9999 -9999 -9999
[11] Dose Effect2 NEGATIVE_RESPONSE
[12+] 0 5 95
 50 10 90
 100 33 67
 150 67 33
```

```
 200 93 7

[5] 5 2 Dichotomous.dax
[6a-6h] 500 1.00E-08 1.00E-08 0 1 1 0 0
[7a-7c] 0.01 0 0.95
[8] -9999 -9999 -9999
[9] 0
[10] -9999 -9999 -9999
[11] Dose Effect3 NEGATIVE_RESPONSE
[12+] 0 1 99
 50 68 32
 100 78 22
 150 88 12
 200 98 2
```

MULTISTAGE DICHOTOMOUS MODEL INPUT FILE

[1] Model name, in this case, the string Multistage

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6] Degree of Polynomial

[7a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[7b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[7c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[8] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[9] Restrict Betas >= 0

= 1 if Restrict Betas >= 0 box is checked

= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Beta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18+] Etc. for Beta3, Beta4 . . .

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[20] Background Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Beta1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Beta2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22+] Etc. for Beta3, Beta4, …as necessary

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Multistage
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5-6] 4 2
```

```
[7-12] 250 2.22045e-16 1.49012e-8 1 0 0 1 1
[13-15] 0.10 0 0.95
[16-18+] -9999 -9999 -9999 …
[19] 0
[20-22+] -9999 -9999 -9999 …
[23-25] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions
Multistage (Polynomial) Model Description

NCTR NESTED MODEL INPUT FILE

[1] Model name, in this case, the string NCTR

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Fixed Size

= 1 if Ctrl Group Mean selected

= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Bootstrap Iterations

= User input value (or default of 1000)

[17] Seed

= If specified, user input value in decimal format (or default of 0)

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Beta Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Theta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Theta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Phi3 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[26+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[27] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[28] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29] Rho Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[30] Beta Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[31] Theta1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[32] Theta2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[33] Phi1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[34] Phi2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[35] Phi3 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[36+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[37] Dose Name

[38] Response Name

[39] Constant String: NEGATIVE_RESPONSE

[40] Litter Specific Covariate

[41] Column 5 name

Data

Dose in first column

Response in Second

Total (Litter Size) minus Response in third column

Litter Size

Example Format

```
[1] NCTR
[2] BMDS MODEL RUN
[3] C:\usepa\BMDS260\Data\Nested.dax
[4] C:\usepa\BMDS260\Data\nct_Nested_Opt.out
[5-5a] 39 4
[6-12] 500 1.00E-08 1.00E-08 0 1 1 0 0 0
[13-17] 0.1000 0 0.95 1000 0
[18-22] -9999 -9999 -9999 -9999 -9999
[23-26+] -9999 -9999 -9999 -9999
[27] 0
[28-32] -9999 -9999 -9999 -9999 -9999
[33-36+] -9999 -9999 -9999 -9999
[37-41] Dose Resp Negative_Resp Covariate Column 5
0 1 15 16 -9999
0 1 8 9 -9999
0 2 13 15 -9999
0 3 11 14 -9999
0 3 10 13 -9999
0 0 9 9 -9999
0 2 8 10 -9999
0 2 12 14 -9999
0 1 9 10 -9999
0 2 9 11 -9999
25 4 10 14 -9999
25 5 4 9 -9999
25 6 8 14 -9999
25 2 7 9 -9999
```

```
25 6 7 13 -9999
25 3 9 12 -9999
25 1 9 10 -9999
25 2 8 10 -9999
25 4 7 11 -9999
25 3 11 14 -9999
50 4 7 11 -9999
50 5 6 11 -9999
50 5 9 14 -9999
50 4 7 11 -9999
50 5 5 10 -9999
50 4 7 11 -9999
50 5 5 10 -9999
50 6 9 15 -9999
50 2 5 7 -9999
50 4 10 14 -9999
100 6 5 11 -9999
100 6 8 14 -9999
100 8 4 12 -9999
100 7 6 13 -9999
100 8 4 12 -9999
100 6 8 14 -9999
100 6 5 11 -9999
100 5 3 8 -9999
100 4 6 10 -9999
```

See also:

Input File Format Description

NCTR Model Description

POLYNOMIAL CONTINUOUS MODEL INPUT FILE

[1] Model Name, in this case, the constant string Polynomial

[2] User Notes

[3] Input file name

[4] Output data file name

[4a] Degree of polynomial

= Default of 2 if user does not input a value

= 1 if Linear model is chosen

= User input value otherwise

[5] Input type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)

= 0 if individual animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)

= 1 if Up (dose-response curve trends up with increasing dose)

= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[10] Restriction on polynomial coefficients

= 0 if none

= -1 if non-positive

= 1 if non-negative

[11] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[13] Smooth Option

= 0 if Unique

= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.

= 1 if Std. Dev

= 2 if Relative Dev.(Default)

= 3 if Point

= 4 if Extra

[15] BMR (BMR Level)

= User input value (or default of 0.1)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)

= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18]-[22+] Parameter values, either user specified or default values. If the parameter is not specified, the default value is -9999

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= user input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20]-[22+] Beta parameters in order of appearance on option screen.

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[24] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[25] Rho Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[26]-[28+] Beta parameters in order of appearance on option screen

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29]-[32] IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:

If Group data is entered:

[29]	[30]	[31]	[32]
Dose name	N name	Mean Name	Std Name

If Individual data is entered:

[29]	[30]
Dose name	Response name

In the same column order as above, this should just be a data listing.

Example Format

```
[1] Polynomial
[2] BMDS MODEL RUN
[3] Poly1.SET
[4] Poly
[4a] 2
```

```
[5-7] 1 6 0
[8-13] 250 2.22045e-16 1.49012e-8 1 0 1 1 0
[14-17] 1 1.00 1 0.95
[18-22+] -9999 -9999 -9999 -9999 -9999
[23] 0
[24-28+] -9999 -9999 -9999 -9999 -9999
[29-32] DOSE NI MEAN STD
0 4 38.45 1.1683
8 5 39.56 1.28218
20 4 40.9 1.303
30 4 41.95 1.418203
40 4 42.725 1.438
50 5 43.42 1.45932
```

See also:

Input File Format Descriptions
Linear Model Description
Polynomial Model Description

POWER CONTINUOUS MODEL INPUT FILE

[1] Model Name, in this case, the constant string Power

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)

= 0 if animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)

= 1 if Up (dose-response curve trends up with increasing dose)

= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[10] Restrict power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[11] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[13] Smooth Option

= 0 if Unique

= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.

= 1 if Std. Dev.

= 2 if Relative Dev.(Default)

= 3 if Point

= 4 if Extra

[15] BMR (BMR Level)

= User input value (or default of 1.000)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)

= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Control Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Power Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[24] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[25] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[26] Control Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[27] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[28] Power Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29]-[32] IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:

If Group data is entered:

29	30	31	32
Dose name	N name	Mean Name	Std Name

If data is entered:

29	30
Dose name	Response name

etc.

In the same column order as above, this should just be a data listing.

Format Example

```
[1] Power
[2] BMDS MODEL RUN
[3] Power.SET
[4] Power
[5-7] 1 6 1
[8-13] 250 2.22045e-16 1.49012e-8 1 0 1 1 0
[14-17] 1 1.00 1 0.95
```

```
[18-22] -9999 -9999 -9999 -9999 -9999
[23] 0
[24-28] -9999 -9999 -9999 -9999 -9999

[29-32] DOSE NI MEAN STD
0 4 38.45 1.1683
8 5 39.56 1.28218
20 4 40.9 1.303
30 4 41.95 1.418203
40 4 42.725 1.438
50 5 43.42 1.45932
```

See also:

Input File Format Descriptions

Power Model Description

PROBIT AND LOG-PROBIT DICHOTOMOUS MODEL INPUT FILES

[1] Model name, in this case, the string Probit

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Log transformation

= 1 if Log transformation is to be used

= 0 otherwise

[9] Restrict Slope

= 1 if Restrict Slope >= 1 box is checked (only appropriate for log-probit model)

= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value or if Log transformation not selected

[17] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Intercept Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[20] Background Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected or if Log transformation not selected

[21] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Intercept Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Probit
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6-12] 250 2.22045e-16 1.49012e-8 1 0 0 1 1 0
[13-15] 0.10 0 0.95
```

```
[16-18] -9999 -9999 -9999
[19] 0
[20-22] -9999 -9999 -9999
[23-25] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

Probit Models Description

Log-Probit Models Description

QUANTAL LINEAR DICHOTOMOUS MODEL INPUT FILE

[1] Model name, in this case, the string QuantalLinear

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] This parameter is set to 0 by the user interface, but is ignored when running the Quantal Linear model.

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file.

[11] Smooth Option

= 0 if Unique

= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra

= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power parameter—for the Quantal Linear model, Power is set to a constant value of 1, regardless of what appears here in the input file.

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[19] Background Parameter.

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[20] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Power Parameter—Constant value -9999 for Quantal Linear model.

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] QuantalLinear
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6-11] 250 2.22045e-16 1.49012e-8 1 1 1 1 0
[12-14] 0.10 0 0.95
[15-17] -9999 -9999 1
[18] 0
[19-21] -9999 -9999 -9999
[22-24] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

Quantal Linear Model Description

RAI AND VAN RYZIN NESTED MODEL INPUT FILE

[1] Model name, here constant string RaiVR

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Fixed Size

= 1 if Ctrl Group Mean selected

= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Bootstrap Iterations

= User input value (or default of 1000)

[17] Seed

= If specified, user input value in decimal format (or default of 0)

[18] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Beta Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Theta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Theta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Phi3 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[26+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[27] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[28] Alpha Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[29] Rho Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[30] Beta Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[31] Theta1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[32] Theta2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[33] Phi1 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[34] Phi2 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[35] Phi3 Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[36+] Phi4 through Phi10 if necessary (as many Phi parameters as dose groups)

= User specified initial value if “initialized” is selected for this parameter

= -9999 if not checked

[37] Dose Name

[38] Response Name

[39] Constant String: NEGATIVE_RESPONSE

[40] Litter Specific Covariate

[41] Column 5 name

Data

Dose in first column

Response in Second

Total (Litter Size) minus Response in third column

Litter Size

Example Format

```
[1] Rai_and_Van_Ryzin
[2] BMDS MODEL RUN
[3] C:\usepa\BMDS260_alpha111014_b\Data\Nested.dax
[4] C:\usepa\BMDS260_alpha111014_b\Data\rvr_Nested_Opt.out

[5-5a] 39 4
[6-12]
```

```
500 1.00E-08 1.00E-08 0 1 1 0 0 0
[13-17] 0.1000 0 0.95 1000 0
[18-22] -9999 -9999 -9999 -9999 -9999
[23-26+] -9999 -9999 -9999 -9999
[27] 0
[28-32] -9999 -9999 -9999 -9999 -9999
[33-36+] -9999 -9999 -9999 -9999
[37-41] Dose Resp Negative_Resp Covariate Dose_Group
0 1 15 16 -9999
0 1 8 9 -9999
0 2 13 15 -9999
0 3 11 14 -9999
0 3 10 13 -9999
0 0 9 9 -9999
0 2 8 10 -9999
0 2 12 14 -9999
0 1 9 10 -9999
0 2 9 11 -9999
25 4 10 14 -9999
25 5 4 9 -9999
25 6 8 14 -9999
25 2 7 9 -9999
25 6 7 13 -9999
25 3 9 12 -9999
25 1 9 10 -9999
25 2 8 10 -9999
25 4 7 11 -9999
25 3 11 14 -9999
50 4 7 11 -9999
50 5 6 11 -9999
50 5 9 14 -9999
50 4 7 11 -9999
50 5 5 10 -9999
```

```
50 4 7 11 -9999
50 5 5 10 -9999
50 6 9 15 -9999
50 2 5 7 -9999
50 4 10 14 -9999
100 6 5 11 -9999
100 6 8 14 -9999
100 8 4 12 -9999
100 7 6 13 -9999
100 8 4 12 -9999
100 6 8 14 -9999
100 6 5 11 -9999
100 5 3 8 -9999
100 4 6 10 -9999
```

See also:

Input File Format Descriptions
Ray and Van Ryzin Model Description

WEIBULL DICHOTOMOUS MODEL INPUT FILE

[1] Model name, in this case, the string Weibull

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[11] Smooth Option

= 0 if Unique

= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra

= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[19] Background Parameter.

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[20] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Power Parameter

= user specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

etc.

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Weibull
[2] BMDS MODEL RUN
[3] EXAMPLE.SET
[4] EXAMPLE
[5] 4
[6-11] 250 2.22045e-16 1.49012e-8 1 1 1 1 0
[12-14] 0.10 0 0.95
[15-17] -9999 -9999 -9999
```

```
[18] 0
[19-21] -9999 -9999 -9999
[22-24] Dose Resp NEGATIVE_RESPONSE
0 3 47
50 6 44
100 10 40
150 19 31
```

See also:

Input File Format Descriptions

Weibull Model Description

WEIBULL DICHOTOMOUS ALTERNATIVE MODEL WITH BACKGROUND DOSE INPUT FILE

[1] Model name, in this case, the string Weibull

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 500 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.00E-08 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict power >= 1

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

> ***Note*** This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file.

[11] Smooth Option

= 0 if Unique

= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra

= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[19] Background Parameter.

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[20] Slope Parameter

= User specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[21] Power Parameter

= user specified initial value if “initialized” is selected for this parameter

= -9999 if “initialized” is not selected

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

etc.

Data

Dose in first column

Response in Second

Total minus Response in third column

Example Format

```
[1] Weibull-BgDose
[2] BMDS_MODEL_RUN
[3] C:\usepa\BMDS250\Data\Dichotomous.dax
[4] C:\usepa\BMDS250\Data\web_Dichotomous_Opt.out
[5] 5
[6-11] 500 1.00E-08 1.00E-08 0 1 1 0 0
[12-14] 0.1000 0 0.95
[15-17] -9999 -9999 -9999
[18] 0
[19-21] -9999 -9999 -9999
[22-24] Dose Effect NEGATIVE_RESPONSE
0 0 100
50 5 95
```

```
100 30 70
150 65 35
200 90 10
```

See also:

Input File Format Descriptions

Weibull Model Description

APPENDIX B: MODEL OPTIONS SCREEN REFERENCE

DICHOTOMOUS MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Dose
- # Subjects in Dose Group
- Incidence
- % Positive

OPTIMIZER ASSIGNMENTS

Specify information controlling the determination of convergence of the model runs. In general, you can safely leave these settings at their default values.

Table 30: *Dichotomous model optimization parameters*

Parameter	Function
Iteration	An upper limit to the number of iterations that will be used in the optimizations (default = 250).
Relative Function	This specifies the criterion for ascertaining relative function convergence (default = 1.0e-8).
Parameter Function	This specifies the criterion for ascertaining parameter convergence (default = 1.0e-8).

PARAMETER ASSIGNMENTS

Choose one of three values related to the displayed parameters. **Note:** Not all models have these parameters.

The parameters are:

- Background
- Slope

- Power
- Intercept
- Beta 1–18

Table 31 describes the value you can select for each parameter.

Table 31: *Dichotomous model parameters*

Values	Function
Default	The initial estimated value for a parameter is determined by the program and its value will vary during optimizations.
Specified	The initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations. See "Parameter Ranges for Dichotomous Models" below.
Initialized	The initial estimated value for a parameter is entered by the user but its value will vary during optimizations. See "Parameter Ranges" below. **If the Initialized option is selected for any parameter, the user must choose the Specified or Initialized option for all parameters.**

Parameter Ranges for Dichotomous Models

- **Background** (if specified or initialized): The Background parameter must be a number ≥0 and ≤1. [Note: not all models have a Background parameter.]
- **Power** (if specified or initialized): The Power parameter must be a positive number, ≤18. If user has chosen to restrict Power, it must also be ≥1; otherwise Power must be >0. [Note: not all models have a Power parameter.
  - **Weibull model**: The Power parameter, if specified or initialized, must be a positive number, ≤18. If the user has chosen to restrict Power, it must also be ≥1; otherwise Power must be greater than or equal to the value the user entered for the Lower Bound on Power (strictly greater than that bound if it is 0).
- **Slope** (if specified or initialized): The Slope parameter must be a number >0. If user has chosen to restrict Slope, it must also be ≥1; otherwise Slope must be >0. [Note: not all models have a Slope parameter.]

OTHER ASSIGNMENTS

Select parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

Table 32: *Dichotomous model parameters for BMD and BMDL calculations*

Parameter	Function
Risk Type	Choices are "Extra" (Default) or "Added." • **Added risk** is the additional proportion of total animals that respond in the presence of the dose, or the predicted probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0). • **Extra risk** is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1—P(0). ***The BMRF for all dichotomous models must be between 0 and 1 (not inclusive).***
BMR	The response, generally expressed as in excess of background, at which a benchmark dose or concentration is desired. User input value (or default of .1000). BMR must be a number >0 and <1.
Confidence Level	The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.
BMD Calculation	Specifies whether or not the user wants a BMD (with associated BMDL) calculated.
BMDL Curve Calc	When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, ***the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary*** (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).
Dose Groups	This is a read-only field indicating the number of Dose groups recorded from the dataset file for input into the model.

Parameter	Function
Restrict Slope >= 1	Models: LogLogistic, Log-Probit, Dichotomous-Hill Selecting this feature (Default for LogLogistic and Dichotomous Hill models) restricts the slope parameter (β) to a value of 1 or greater. • For the LogLogistic and Dichotomous Hill models, if β < 1, the slope of the dose-response curve becomes infinite at the control dose. • For the LogProbit and LogProbit-BgDose models, the slope of the dose-response curve can be very steep at low doses at or below the BMD or BMDL, before it becomes smaller approaching zero dose. Such characteristics, for all four models, may be biologically unrealistic, and can lead to numerical problems.
Restrict Power >= 1	Models: Gamma , Weibull Selecting this feature (Default) restricts the power parameter (α) to a value of 1 or greater. If α < 1, then the slope of the dose-response curve becomes infinite at the control dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so EPA recommends restricting α ≥ 1.
Degree of Polynomial	Models: Multistage, Multistage-Cancer This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 23). The degree must be a positive integer (typically less than the number of dose groups.) A value must be entered here before the model will run. Polynomial degree should not exceed the number of dose groups unless the beta coefficients of the model are specified or restricted (beta coefficients are always restricted in the multistage-cancer model).
Restrict Betas >= 0	Model: Multistage Selecting this feature (Default) restricts all of the beta (β) parameter coefficients in the multistage model to a value of 0 or greater.
Lower Bound on Power	Model: Weibull • If "Restrict Power>=1" is selected, then a default value of 1 is entered. If a zero is entered, then the model should set a lower bound of 1e-8. • If "Restrict Power>=1" is unselected, then enter a non-negative value ≤18.

Note About BMRF and Graphs

The response associated with the BMR that is displayed in the graphical model output will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response value one must solve for P(d) in the equation for added or extra risk. In addition to the two options listed above for all dichotomous models, the following options are available for specific models of the Dichotomous or Dichotomous_Alternative Type.

FILE-RELATED FIELDS

Table 33: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the Set button to change the file name and/or location.

See also:

- Dichotomous and Dichotomous_Alternative Model Option Screens
- Dichotomous Model Descriptions
- Dichotomous Alternative Model Descriptions
- Optimization Criteria

DICHOTOMOUS_ALTERNATIVE MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Dose
- # Subjects in Dose Group
- Incidence
- % Positive

OPTIMIZER ASSIGNMENTS

Specify information controlling the determination of convergence of the model runs. In general, you can safely leave these settings at their default values.

Table 34: *Dichotomous Alternative model optimization parameters*

Parameter	Function
Iteration	An upper limit to the number of iterations that will be used in the optimizations (default = 250).
Relative Function	This specifies the criterion for ascertaining relative function convergence (default = 1.0e-8).
Parameter Function	This specifies the criterion for ascertaining parameter convergence (default = 1.0e-8).

PARAMETER ASSIGNMENTS

Choose one of three values related to the displayed parameters. **Note:** Not all models have these parameters.

The parameters are:

- v
- g
- Background
- Slope
- Power
- Intercept
- Beta 1–18

The following table describes the value you can select for each parameter.

Table 35: *Dichotomous Alternative model parameters*

Values	Function
Default	The initial estimated value for a parameter is determined by the program and its value will vary during optimizations.
Specified	The initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations. See “Parameter Ranges” below.
Initialized	The initial estimated value for a parameter is entered by the user but its value will vary during optimizations. See “Parameter Ranges for Dichotomous Models” below. **If the Initialized option is selected for any parameter, you must choose the Specified or Initialized option for all parameters.**

Parameter Ranges for Dichotomous Models

- **v** (if specified or initialized): The parameter v must be a number ≥0 and ≤1. [Note: not all models have a v parameter.]
- **g** (if specified or initialized): The parameter g must be a number ≥0 and ≤1. [Note: not all models have a g parameter.]
- **Background** (if specified or initialized): The Background parameter must be a number ≥0 and ≤1. [Note: not all models have a Background parameter.]
- **Power** (if specified or initialized): The Power parameter must be a positive number, ≤18. If user has chosen to restrict Power, it must also be ≥1; otherwise Power must be >0. [Note: not all models have a Power parameter.
  - **Weibull model**: The Power parameter, if specified or initialized, must be a positive number, ≤18. If the user has chosen to restrict Power, it must also be ≥1; otherwise Power must be greater than or equal to the value the user entered for the Lower Bound on Power (strictly greater than that bound if it is 0).
- **Slope** (if specified or initialized): The Slope parameter must be a number ≥0. If user has chosen to restrict Slope, it must also be ≥1; otherwise Slope must be ≥0. [Note: not all models have a Slope parameter.]

OTHER ASSIGNMENTS

Select parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

Table 36: *Dichotomous Alternative model parameters for BMD and BMDL calculations*

Parameter	Function
Risk Type	Choices are "Extra" (Default) or "Added." • **Added risk** is the additional proportion of total animals that respond in the presence of the dose, or the predicted probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0). • **Extra risk** is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1—P(0). ***The BMRF for all dichotomous models must be between 0 and 1 (not inclusive).***
BMR	The response, generally expressed as in excess of background, at which a benchmark dose or concentration is desired. User input value (or default of .1000). BMR must be a number >0 and <1.
Confidence Level	The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.

Parameter	Function
BMD Calculation	Specifies whether or not the user wants a BMD (with associated BMDL) calculated.
BMDL Curve Calc	When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, ***the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary*** (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).
Dose Groups	This is a read-only field indicating the number of Dose groups recorded from the dataset file for input into the model.
Restrict Slope >= 1	Models: LogLogistic, Log-Probit, Dichotomous-Hill Selecting this feature (Default for LogLogistic and Dichotomous Hill models) restricts the slope parameter (β) to a value of 1 or greater. • For the LogLogistic and Dichotomous Hill models, if $\beta < 1$, the slope of the dose-response curve becomes infinite at the control dose. • For the LogProbit and LogProbit-BgDose models, the slope of the dose-response curve can be very steep at low doses at or below the BMD or BMDL, before it becomes smaller approaching zero dose. Such characteristics, for all four models, may be biologically unrealistic, and can lead to numerical problems.
Restrict Power >= 1	Models: Gamma , Weibull Selecting this feature (Default) restricts the power parameter (α) to a value of 1 or greater. If $\alpha < 1$, then the slope of the dose-response curve becomes infinite at the control dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so EPA recommends restricting $\alpha \geq 1$.
Degree of Polynomial	Models: Multistage, Multistage-Cancer This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 23). The degree must be a positive integer (typically less than the number of dose groups.) A value must be entered here before the model will run. Polynomial degree should not exceed the number of dose groups unless the beta coefficients of the model are specified or restricted (beta coefficients are always restricted in the multistage-cancer model).
Restrict Betas >= 0	Model: Multistage Selecting this feature (Default) restricts all of the beta (β) parameter coefficients in the multistage model to a value of 0 or greater.

Parameter	Function
Lower Bound on Power	Model: Weibull • If "Restrict Power>=1" is selected, then a default value of 1 is entered. • If "Restrict Power>=1" is unselected, then enter a value from 0-.

Note About BMRF and Graphs
The response associated with the BMR that is displayed in the graphical model output will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response value one must solve for P(d) in the equation for added or extra risk. In addition to the two options listed above for all dichotomous models, the following options are available for specific models of the Dichotomous or Dichotomous_Alternative Type.

FILE-RELATED FIELDS

Table 37: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the **Set** button to change the file name and/or location.

See also:

- Dichotomous and Dichotomous_Alternative Model Option Screens
- Dichotomous Model Descriptions
- Dichotomous Alternative Model Descriptions
- Optimization Criteria

CONTINUOUS MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Dose
- # Subjects in Dose Group
- Mean
- Std. Deviation
- Response

PARAMETER ASSIGNMENTS

Choose one of three values related to the displayed parameters. **Note:** Not all models have these parameters.

The parameters are:

- Alpha
- Rho
- Control
- Slope
- Power
- Beta 0–18
- v
- n
- k

The following table describes the value you can select for each parameter.

Table 38: *Continuous model option parameters*

Values	Function
Default	The initial estimated value for a parameter is determined by the program and its value will vary during optimizations.
Specified	The initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations. See “Parameter Ranges” below.
Initialized	The initial estimated value for a parameter is entered by the user but its value will vary during optimizations. See “Parameter Ranges for Continuous Models” below. **If the Initialized option is selected for any parameter, you must choose the Specified or Initialized option for all parameters.**

Parameter Ranges for Continuous Models

- **n** (if specified or initialized): The parameter n must be a positive number. Also consider its restriction).
- **k** (if specified or initialized): The parameter k must be a positive number.
- **Power**: (if specified or initialized): The Power parameter must be a positive number, ≤18. If user has chosen to restrict Power, it must also be ≥1; otherwise Power must be >0.

OTHER ASSIGNMENTS

Select parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

Table 39: *Continuous model parameters for BMD and BMDL calculations*

Parameter	Function
Adverse Direction	Refers to whether adversity increases as the dose-response curve rises "up" or falls "down." Choices are "Automatic" (Default), "Up," or "Down." If automatic is chosen, the software chooses the adverse direction based on the shape of the dose-response curve. However, you can manually choose the adverse direction if you know the direction of adversity for the endpoint being studied. This selection only impacts how the user-designated BMR is used in conjunction with model results to obtain the BMD.

Parameter	Function
BMR Type	The method of choice for defining the response level used to derive the benchmark dose (BMD). • **Rel. Dev.** (Relative Deviation) means the response associated with the BMR will be the background estimate plus or minus (depending on the Adverse Direction) the product of the background estimate times the BMRF entered by the user. • **Abs. Dev.** (Absolute Deviation) means the response associated with the BMR will be the background estimate plus or minus the BMRF. • **Std. Dev.** (Standard Deviation) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the standard deviation for the control group data. • **Point** means the response associated with the BMR will be the BMRF value itself. • **Extra** (Hill model only) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the difference between the background estimate and the model estimate of the maximum/minimum response. "Extra" is similar to Extra risk for dichotomous data, except that the maximum (or minimum) achievable response is not 1, but is estimated from the model. For more information on the mathematical formula behind each choice, see Continuous Model Option Screen. When response data is lognormally distributed, the BMR Types acquire different meanings. As of BMDS 2.4, only continuous exponential models can assume lognormal distribution. For more information, refer to Unique Options for Exponential Models.
BMRF	The factor defining the benchmark response level. Its value will depend on the Risk Type or BMR Type specified by the user (one of these types will also be in the Other Assignments section, depending on the model type). BMRF must be a positive number. If the BMR Type is "Extra," BMRF must also be >0 and <1.
Confidence Level	The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.
Constant Variance	When selected (Default), the model assumes a constant variance across all dose groups. If not selected, then the model assumes that the variance can be different for each dose group, and varies as a power function of the mean response (see Continuous Model Descriptions for more details).
BMD Calculation	Specifies whether or not the user wants a BMD (with associated BMDL) calculated.

The following options are available for specific continuous models.

Table 40: *Options for specific continuous models*

Parameter	Function
Degree of Polynomial	Models: Linear, Polynomial This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 21). A value must be entered here before the model will run. Polynomial degree should be a positive integer and should not exceed the number of dose groups unless the beta coefficients of the model are restricted. For the linear model, this field is set to 1 and is not editable.
Restrict Power >= 1	Models: Power, Exponential The power parameter can be restricted to be greater than or equal to one. The power is unrestricted if this option is not selected. This option is currently disabled for the exponential models.
Restrict n>1	Model: Hill The n parameter of the Hill model can be restricted to be greater than one. The n parameter is unrestricted if this option is not selected.
Restriction	Models: Linear, Polynomial Restrictions on coefficients of the dose terms can be “None” (Default), “Non-negative” (>0), or “Non-positive” (<0). Note that, while no restrictions (None) is the current default for this option, the user should specify that the parameters be restricted to either Non-negative or Non-positive values whenever possible to avoid “wavy” model responses (see details in Polynomial Model description). Since there is only one dose coefficient in the continuous Linear model, this is sometimes referred to as restricting the slope of this model.
BMDL Curve Calc	Models: Linear, Polynomial, Power When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, *the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary* (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).

FILE-RELATED FIELDS

Table 41: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the **Set** button to change the file name and/or location.

See also:

- Continuous Exponential Model Options Fields
- Continuous Models—Descriptions
- Unique Options for Exponential Models

CONTINUOUS EXPONENTIAL MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Dose
- # Subjects in Dose Group
- Mean
- Std. Deviation
- Response

OTHER ASSIGNMENTS

Select parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

Table 42: *Continuous Exponential model parameters for BMD and BMDL calculations*

Parameter	Function
Distribution	Specify whether the data are Normally or Lognormally distributed around the dose-group-specific means. The choice of the distribution affects the type of maximum-likelihood estimation (MLE) solution that may be obtained (see the description for the **Solution** option). Moreover, when a lognormal distribution is assumed, only constant (log-scale) variance models will be fit to the data; such models correspond to an assumption of a constant coefficient of variation.
Solution	Choose to get an "Exact" or "Approximate" maximum-likelihood estimation (MLE) solution. When the data are assumed to be ***normally distributed***, the choice is fixed at "Exact" because the exact solution is available no matter how the data are presented (either as group-specific means and variances or as individual responses). When the data are assumed to be ***lognormally distributed*** and the data are presented in terms of group-specific means and standard deviations, then the exact MLE solution cannot be obtained. In that case, the "Solution" option is fixed at "Approximate" and the means and standard deviations of the log-transformed data are estimated as follows: log-scale mean = ln(mean)—ln(1+(std/mean)2)/2 log-scale std = sqrt[ln(1+(std/mean)2)] When the data are assumed to be lognormally distributed and the individual responses are available the user may choose between the exact and approximate solutions. In this case, the user is advised to select the exact solution; the only reason to select the approximate solution in this case would be to compare it to other calculations that were done approximately out of necessity.
Confidence Level	The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.
Constant Variance	When selected (Default), the model assumes a constant variance across all dose groups. If not selected, then the model assumes that the variance can be different for each dose group, and varies as a power function of the mean response (see Continuous Model Descriptions for more details).
BMD Calculation	Specifies whether or not the user wants a BMD (with associated BMDL) calculated.
Restrict Power >= 1	The power parameter can be restricted to be greater than or equal to one. The power is unrestricted if this option is not selected. This option is currently disabled for the exponential models.

Parameter	Function
Adverse Direction	Refers to whether adversity increases as the dose-response curve rises "up" or falls "down." Choices are "Automatic" (Default), "Up," or "Down." If automatic is chosen, the software chooses the adverse direction based on the shape of the dose-response curve. However, you can manually choose the adverse direction if you know the direction of adversity for the endpoint being studied. This selection only impacts how the user-designated BMR is used in conjunction with model results to obtain the BMD.
BMR Type	The method of choice for defining the response level used to derive the benchmark dose (BMD). • **Rel. Dev.** (Relative Deviation) means the response associated with the BMR will be the background estimate plus or minus (depending on the Adverse Direction) the product of the background estimate times the BMRF entered by the user. • **Abs. Dev.** (Absolute Deviation) means the response associated with the BMR will be the background estimate plus or minus the BMRF. • **Std. Dev.** (Standard Deviation) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the standard deviation for the control group data. • **Point** means the response associated with the BMR will be the BMRF value itself. • **Extra** (Hill model only) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the difference between the background estimate and the model estimate of the maximum/minimum response. "Extra" is similar to Extra risk for dichotomous data, except that the maximum (or minimum) achievable response is not 1, but is estimated from the model. For more information on the mathematical formula behind each choice, see Continuous Model Option Screen. When response data is lognormally distributed, the BMR Types acquire different meanings. As of BMDS 2.4, only continuous exponential models can assume lognormal distribution. For more information, refer to Unique Options for Exponential Models.
BMRF	The factor defining the benchmark response level. Its value will depend on the Risk Type or BMR Type specified by the user (one of these types will also be in the Other Assignments section, depending on the model type). BMRF must be a positive number. If the BMR Type is "Extra," BMRF must also be >0 and <1.

Definition of BMR Types under Lognormal Distribution Assumption

The Exponential models allow the user to assume that the response data are lognormally distributed, with median values defined by the dose-response function and a constant log-scale variance. Under such an assumption the BMR

types are defined and implemented so that they are calculated by the program to return BMDs as follows (where BMRF is the numerical value, specified by the user, indicating the response, or change in response, of interest):

- **Relative Deviation**: The natural scale median value at the BMD, m(BMD), differs from the natural scale median at 0 dose, m(0), such that |m(BMD)—m(0)|/m(0) = BMRF.
- **Absolute Deviation**: The natural scale median value at the BMD, m(BMD), differs from the natural scale median at 0 dose, m(0), such that |m(BMD)—m(0)| = BMRF.
- **Standard deviation**: The log-scale mean at the BMD, ln(m(BMD)), differs from the log-scale mean at 0 dose, ln(m(0)), such that |ln(m(BMD))—ln(m(0))|/σ(0) = BMRF, where σ(0) is the log-scale standard deviation at 0 dose. Recall that σ(0) = ln(GSD(0)). This definition allows the user to use BMRF's typical of an analysis where a normal distribution of responses is assumed (e.g., the EPA default of 1 standard deviation) and still maintain the logic and rationale for such choices, since the log-transformed response values under the lognormal assumption would themselves be normally distributed.
- **Point**: The natural scale median value at the BMD, m(BMD), equals the BMRF, i.e., m(BMD) = BMRF.

MODEL SELECTION

The exponential model choice allows you to run up to four models that have exponential-dose terms. These models are referred to as exponential Models 2–5 (following a designation by Dr. Wout Slob, wherein the restricted (flat) model was model 1). Refer to the section on Exponential Continuous Model Description for additional details.

You may choose to run any or all of the exponential models when running from a Session screen. (When running on a single dataset by use of the data grid, all exponential models will be run.) Moreover, you may select to have the exponential model runs reported (grouped) together in one output file or on separate output files.

- **Model 2**
- **Model 3**
- **Model 4**
- **Model 5**
- **Grouped**—Select to have the selected exponential model runs reported (grouped) together in one output file or on separate output files.

FILE-RELATED FIELDS

Table 43: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the **Set** button to change the file name and/or location.

See also:

- Continuous Models—Descriptions
- Exponential Continuous Model Description
- Continuous Model Options Fields
- Unique Options for Exponential Models

NESTED MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Dose
- Litter Size
- Incidence
- Litter Specific Covariate

OPTIMIZER ASSIGNMENTS

Specify information controlling the determination of convergence of the model runs. In general, you can safely leave these settings at their default values.

Table 44: *Nested model optimization parameters*

Parameter	Function
Iteration	An upper limit to the number of iterations that will be used in the optimizations (default = 250).
Relative Function	This specifies the criterion for ascertaining relative function convergence (default = 1.0e-8).
Parameter Function	This specifies the criterion for ascertaining parameter convergence (default = 1.0e-8).

PARAMETER ASSIGNMENTS

Choose one of three values related to the displayed parameters. **Note:** Not all models have these parameters.

The parameters are:

- Alpha
- Rho
- Beta
- Theta1
- Theta2
- Phi1–10

The following table describes the value you can select for each parameter.

Table 45: *Nested model parameter assignments*

Values	Function
Default	The initial estimated value for a parameter is determined by the program and its value will vary during optimizations.
Specified	The initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations. See “Parameter Ranges” below.
Initialized	The initial estimated value for a parameter is entered by the user but its value will vary during optimizations. See “Parameter Ranges for Nested Models” below. **If the Initialized option is selected for any parameter, you must choose the Specified or Initialized option for all parameters.**

Parameter Ranges for Nested Models

Any **Phi** (if specified or initialized): Phi must be a number ≥0 and ≤1.

OTHER ASSIGNMENTS

Select parameter constraints and choices for BMD and BMDL calculations. All models contain the following fields in the Other Assignments section.

Table 46: *Nested model parameters for BMD and BMDL calculations*

Parameter	Function
Risk Type	Choices are "Extra" (Default) or "Added." • **Added risk** is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0). • **Extra risk** is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1—P(0). Thus, extra and additional risk are equal when background rate is zero.
Fixed Litter Size	Choices are "Control Group Mean" (Default) or "Overall Mean." See Nested Model Descriptions for an explanation as to why this option is necessary, and which choice would be preferred for your given dataset. Basically, if the Litter Specific Covariate is not affected by dose, the Overall Mean should be used. If the Litter Specific Covariate is affected by dose, consider using the Control Group Mean.
Litter Specific Covariate	Provides user with the option to allow the models to attempt to account for a litter specific covariate or not. • If "Use Litter Specific Covariate" is selected (Default), all of the Theta values are estimated. • If "Don't Use Litter Specific Covariate" is chosen, all of the Theta values are set to zero.
Intralitter Correlations	Provides user with the option to allow the models to attempt to estimate intralitter correlations or assume they are zero. • If "Estimate Intralitter Correlations" is selected (Default), all of the Phi values are estimated (one for each dose group). • If "Assume Intralitter Correlations Zero" is chosen, all of the Phi values are set to zero.
Dose Groups	This is a read-only field indicating the number of Dose groups recorded from the dataset file for input into the model.
Restrict Power>=1	Selecting this feature (Default) restricts the power parameter (α) to a value of 1 or greater. If $\alpha < 1$, then the slope of the dose-response curve becomes infinite at the control dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so EPA recommends restricting $\alpha \geq 1$.
BMD Calculation	Specifies whether or not the user wants a BMD (with associated BMDL) calculated.

Parameter	Function
BMDL Curve Calc	When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line or a curve. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, ***the current default and recommended option is to not request calculation of the BMDL curve unless absolutely necessary*** (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).
BMR	The response, generally expressed as in excess of background, at which a benchmark dose or concentration is desired. User input value (or default of .1000). BMR must be a number >0 and <1.
Confidence Level	The confidence level (default 0.95) associated with the BMDL calculation. Confidence level must be a number >0 and <1.
Bootstrap Iterations	Specify the number of bootstrap iterations (default is 1000) to run to estimate goodness of fit. It is recommended to keep the value at a minimum of 1000.
Specify Bootstrap Seed	Select this feature to specify a bootstrap seed for the random number generator. Default is that BMDS auto-generates a seed for the random number generator based on the system clock.
Seed (Hexadecimal Value)	If **Specify Bootstrap Seed** is selected, enter the value here in hexadecimal form. Example: “1E240”.

FILE-RELATED FIELDS

Table 47: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the **Set** button to change the file name and/or location.

See also:

- Nested Model Options Fields
- Nested Models—Descriptions

REPEATED RESPONSE MEASURES MODEL OPTIONS FIELDS

COLUMN ASSIGNMENTS

Use the picklists to assign columns from the data file to the parameters that are required for model runs.

BMDS expects the following fields to be defined:

- Animal ID
- Dose
- Time
- Response

PLOTTING ASSIGNMENTS

The ToxicoDiffusion model includes graphical outputs showing the observed and model-predicted time-course data, residuals, and a summary of the bootstrap-based BMDL calculations. You can specify the properties of the resulting graphs here. In general, you can safely leave these settings at their default values.

- Chart Title (optional)
- Time Axis Scale: Select either Natural (default) or Log.
- # of Time Points: Default is 100.
- X-Axis Minimum Value
- X-Axis Maximum Value
- Y-Axis Minimum Value
- Y-Axis Maximum Value

PARAMETER ASSIGNMENTS

Choose one of three values related to the displayed parameters. **Note:** Not all models have these parameters.

The parameters are:

- A0
- B0

- C0
- K0
- A1
- A2

The following table describes the value you can select for each parameter.

Table 48: *Repeated Response Measures model option parameters*

Values	Function
Default	Enable the program to find initial values for the optimization runs (the default values of "-9999" shown in the option screen are merely flags to pass to the input file that indicate this default option—they are not real initial values)
Initialized	Initialize the parameter values to values of the user's choice.

OTHER ASSIGNMENTS

Table 49: *Repeated Response Measures model option parameters*

Field	Function
Exposure Time	The time must be a real number ≥ 0. The value should be chosen to be consistent with the timing of the observations as recorded in the data set. For example, if the exposure time is "4.5," then exposure occurred at time 0, with the time of the first observation of a response occurring 4.5 hours later (if hours are the units used to designate the time parameter).
Background Degree	Specify the background degree that determines how the responses are assumed to vary over time in the absence of exposure. This background (without-exposure) variation is defined by a polynomial of the specified degree. Choices are: • 0—Constant (default) • 1—Linear • 2—Quadratic
BMR Risk Type	Choices are : • **Extra risk** (default) is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1—P(0). • **Added risk** is the additional proportion of total animals that respond in the presence of the dose, or the predicted probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0).

Field	Function
BMR Risk Level	The response, generally expressed as in excess of background, at which a benchmark dose or concentration is desired. User input value (or default of .05). It must be a number >0 and <1.
Adverse Direction	Refers to the "tail" of the distribution of the response variable where adverse values are assumed to fall. • **Lowertail** (default) means that low values are indicative of adversity; this is typically associated with a dose-response curve that decreases as exposure to a toxic substance increases. • **Uppertail** means that high values are indicative of adversity; this is typically associated with a dose-response curve that increases as exposure to a toxic substance increases. • **Bothside** indicates that values that are either high or low (i.e., far from the average response) are indicative of adversity; this option is less frequently used
Adverse Definition	Choices are **Background Rate** (default) or **Cut Point**. Adverse responses can be defined in one of two ways. • A background rate (probability) of adverse response is specified (e.g., a 5% rate of adverse response in the absence of exposure). Select Background Rate and then specify the rate in the Adverse Level field. • Specified cut-off value(s), with the assumption that values above or below (depending on the adverse direction) the cut-off(s) are adverse. Select Cut Point to enable the Low Cut-off and High Cut-off fields (which fields are enabled is based on Adverse Direction).
Adverse Level	User-specified or .05 (default) if Adverse Definition = "Background Rate". Field is disabled if Adverse Direction is "Cut Rate." A value of .05 represents a 5% rate of adverse response in the absence of exposure.
Low Cut-off	User-specified or -9999 default. Values below the cut-off are adverse. Enabled when: • Adverse Direction is Lowertail or Bothside • Adverse Definition is Cut Point
High Cut-off	User-specified or -9999 default. Values above the cut-off are adverse Enabled when: • Adverse Direction is Uppertail or Bothside • Adverse Definition is Cut Point
Use Two Sided CI?	Default is unselected (i.e., one-sided). See the description of the Bootstrap Iterations parameter.

Field	Function
Confidence Level	The confidence level (default 0.05) associated with the BMDL calculation. Confidence level must be a number >0 and <1. For "Confidence Level" the user must actually enter a p value such that the level of confidence is (1-p)*100%. For example, a "Confidence Level" value of 0.05 corresponds to requesting 95% confidence limits: (1—0.05)*100% = 95%.
Bootstrap Iterations	Specify the number of bootstrap iterations (default is 100) to run to estimate confidence bounds. The bounds can be one-sided or (if the "Use Two Sided CI?" box is checked) two-sided. The number of bootstrap iterations should be large enough to provide a stable estimate of the bounds. Values on the order of 100 or more will probably be required in most cases; the user should perhaps do several runs to determine that the bound estimates have stabilized for the number of iterations chosen. Increasing the number of iterations will noticeably increase the time it takes to run the model.
Save Bootstrap Result?	Default is unselected (i.e., do not save bootstrap result).

STUDY DESCRIPTION

Supply any additional experiment-specific information to be reported in the output files.

- Chemical Name
- Exposure Type
- Species Name
- Gender

FILE-RELATED FIELDS

Table 50: *File-related fields*

Field	Function
User Notes	An editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.
Data File	A field displaying the name of the data file (*.dax) file.
Out File Name	Displays the output path and file name. Click the **Set** button to change the file name and/or location.

See also:

- Repeated Response Measures Option Screen
- Repeated Response Measures Model Description

APPENDIX C: VERSION HISTORY

The following sections document new, changed, or updated BMDS features as documented in each version's respective readme file. The information is included here for historical and reference purposes.

BMDS 1.2

September 2, 2000—A new user interface (BMDS0900.exe) was distributed to fix some problems with installation of BMDS on certain Windows 98 configurations. If you successfully installed BMDS version 1.2 using a previous installation procedure you do not need this upgrade. This upgrade merely simplifies the installation process and corrects some problems that did not allow BMDS to install to certain computer hardware/software configurations. (This version of the software is no longer being made available as there are newer versions now available which fix problems that were being encountered on newer operating systems.)

BMDS 1.2.1

October 25, 2000—A new version of BMDS, version 1.2.1, is being distributed at this time. This version contains new versions of the continuous Polynomial (version 2.1) and Hill (version 2.1) models. If you do not want to completely reinstall BMDS, you can download the the new model executables (see Latest Versions of BMDS Help and Model Files) and run them separately or under the BMDS version 1.2 interface. These new versions of the polynomial and Hill models fix problems associated with running the model on Windows NT/2000 operating systems, provide improved model fit for certain unique data sets and improve upon the rate of convergence on a BMD and BMDL.

BMDS 1.3

March 22, 2001—Version 1.3 of BMDS is now available! This latest version of BMDS, version 1.3, contains new continuous Polynomial (v2.1), Power (v2.1) and Hill (v2.1) models, new dichotomous Multistage (v2.1), Weibull (v2.1) and Gamma (v2.2) models, and an improved user interface. The new models are more compact and stable (will converge on BMD and BMDL solutions more often). The user interface upgrades are described in the new help manual (PDF format) for version 1.3 and the readme.txt file that is distributed with the upgrade.

BMDS 1.3.1

January 22, 2002—Version 1.3.1 of BMDS is now available! Version 1.3.1 contains a revised help manual and user interface, including a revision to the interface that allows the Multistage model to calculate BMD and BMDL values for very low (below E-5) benchmark response (BMR) levels.

November 13, 2002—A new polynomial model (Version 2.2) is now available that fixes the previous incompatibility with Windows 2000. Download it to your main bmds directory (same directory as the bmds.exe file).

BMDS 1.3.2

May 23, 2003—Version 1.3.2 of BMDS is now available! Version 1.3.2 contains revised polynomial (poly.exe) and nested logistic (nlogist.exe) models that are compatible with Windows 2000. If you are using a Windows 98 or older operating system, you may need to update your msvcrt.dll driver. We suggest that you obtain the latest msvcrt.dll driver from Microsoft or download this version of the msvcrt.dll driver and copy it to the c:\windows\system directory of your computer (you may have to exit Windows and do this in DOS mode).

BMDS 1.4.1

February 5, 2007—Version 1.4.1 is now available! All models have been recompiled to improve speed, stability and compatibility with the latest Windows operating systems. Improvements have been made to the model output format for all models. A Multistage-Cancer model has been added that calculates and reports a cancer slope factor and plots the linear extrapolation from the BMDL to the background response estimate per EPA's 2005 cancer guidelines. Unlike the Multistage model, the Multistage Cancer model does not estimate added risk, nor does it allow beta coefficients to be unrestricted. The Quantal-Quadratic model was removed from Dichotomous model choices (note: the user can still run this model by specifying the power term of the Weibull model to be 2, but this model is not retained in the BMDS dichotomous model listings)

Issues in the continuous models that caused occasional errors in degrees of freedom assignments which impacted continuous model test results have been resolved. Acceptance criteria for Tests 2, 3 and 4 was changed from p>=0.05 to p>=0.1 and default risk type changed to “Std. Dev.” for all continuous models to be consistent with EPA's draft BMD technical guidance (EPA, 2000). Issues with the Hill model have been fixed, including memory problems which were causing some operating systems to crash. Parameter standard error estimates and Chi-squared residual calculations in all the continuous models were checked and

corrected if in error. Model A3 of the continuous model testing procedures has been modified so that it always uses the user-specified value for the parameter rho, including the constant-variance case where rho = 0. When rho = 0, model A3 is the same as model A1, and it is reported explicitly in the constant-variance runs. As a consequence, all model runs report the entire set of models (A1, A2, A3, R and the fitted model) and all four hypothesis tests.

Issues in the Nested models that caused occasional errors in degrees of freedom assignments have been resolved. Memory problems which were causing problems for some NCTR model runs have been fixed.

August 29, 2007—BMDS Version 1.4.1b has been added to replace version 1.4.1. This version contains an update to the BMDS help file.

November 9, 2007—BMDS version 1.4.1c is now available. This version updates dichotomous models that were already included on BMDS version 1.4.1b. The updates primarily improve the handling of parameter specifications, particularly in situations where the user may wish to specify the background parameter to be zero.

BMDS 2.0 (BETA)

September 28, 2007—BMDS Version 2.0 beta is now available for inspection and testing (NOTE: this is a beta test version, provided only for your examination and testing—BMDS 1.4.1b should be used for definitive risk assessment calculations). BMDS 2.0 beta employs a new graphical user interface and makes it easy to run a number of models for one data set and compare the results. BMDS 2.0 beta also has a new set of quantal models with alternative background parameters (i.e., background additive to dose). We welcome comments and suggestions on the functioning of the interface and its new features, and on the new models.

October 10, 2007—BMDS 2.0 beta—Build 19 released on October 10, 2007 replaces the first BMDS 2.0 beta release of September 28, 2007 (Build 13). The new Build 19 has important changes and enhancements as a result of additional testing and user exposure and should be downloaded and used instead of Build 13. Enhancements include the ability to better run a number of the BMD models and also added flexibility and fixes for user interface features. Changes include the designation of the new Dichotomous models as Alternate Dichotomous to better reflect their production status. Please refer to the readme.txt file included with the software installation for more details on the BMDS 2.0 beta.

BMDS 2.0 (FINAL)

July 10, 2008—BMDS Version 2.0 final is now available. Released on July 10, 2008, it replaces BMDS 1.4.1c as the official BMDS software. BMDS 2.0 is a rewrite of the user interface and risk assessment modeling framework, with a markedly improved functionality and enhanced multi-model processing capabilities. It uses the same underlying source code for the models in BMDS 1.4.1 software, with minor corrections and some important additions. For details on the new user interface, go to the BMDS 2.0 Help menu option in the installed software. BMDS 2.0 also has a new set of quantal models with alternative background (i.e., background additive to dose) and asymptote (i.e., Hill model) parameters, as well as a Beta Exponential set of models.

BMDS 2.1 (BETA)

September 30, 2008—EPA is making version 2.1 of BMDS available at this time for public beta testing. Version 2.1 includes a beta (external peer review) version of a new time-dependent toxicodiffusion model for continuous outcomes (Zhu et al., 2005), incorporates graphical plots for the continuous exponential models and allows for the use of individual animal continuous response data. The BMDS toxicodiffusion model was developed by the USEPA National Center for Environmental Assessment (NCEA), through partnerships with the USEPA Neurotoxicology Division (NTD) and the University of South Florida, to characterize toxic effects (e.g., neurotoxicity) that potentially evolve along critical time points. It does this by:

- modeling a dose-response along a time-course of repeated response measures; and
- computing benchmark doses and their confidence limits along the time course.

Documentation for the toxicodiffusion model can also be downloaded. The documentation contains a full description of the model, input requirements, model run options and sample runs.

In addition, EPA is distributing an external review (beta) version of a concentration-time (CxT) model originally programmed by Wil ten Berge. The EPA ten Berge model implements an approach to evaluating the CxT relationships for effects associated with chemical exposures. The EPA's version 1.0 implementation of this model is being distributed along with associated documentation and comments on the model received from external peer reviewers. EPA plans to respond to external review comments and incorporate the ten Berge model into a future version of BMDS.

BMDS 2.1 (BUILD 52)

July 30, 2009—EPA is now distributing the final release of Version 2.1 (Build 52) of the Benchmark Dose Software (BMDS). BMDS 2.1 (Build 52) contains user interface enhancements as well as several additions/enhancements to the suite of models available for modeling dose-response data, including new features for the continuous exponential models and a new interface for the ten Berge concentration-time model. For details on the changes to the user interface, go to the BMDS 2.1 Help menu option in the installed software. The Readme.rtf file distributed with BMDS describes the improvements made in version 2.1 (Build 52), installation requirements, and known problems.

The exponential models contained in this version of BMDS have been developed in conjunction with the Netherlands' National Institute for Public Health and the Environment (RIVM) to be consistent with the exponential models contained in the RIVM's PROAST software . The USEPA and RIVM are working together to achieve consistency between the BMDS and PROAST software and methods.

BMDS 2.1.1 (BUILD 55)

November 9, 2009—EPA is now distributing Version 2.1.1 (Build 55) of the Benchmark Dose Software (BMDS). BMDS 2.1.1 (Build 55) contains a flexible new feature that allows users to export select BMDS summary report data and plots to Excel. It also contains a comprehensive set of sample session and model option files to assist users in running batch operations, and several improvements to the ten Berge model that were not available in version 2.1. The Readme.rtf file distributed with BMDS provides details on the improvements made in Version 2.1.1 (Build 55), installation requirements, and known problems.

BMDS 2.1.2 (BUILD 60)

June 11, 2010—BMDS 2.1.2 (Build 60) contains user interface enhancements to the “Summary Report” feature, new sample session and model option files, and improvements to the ten Berge model that were not available in version 2.1.1:

- BMDS 2.1.2 can access folders or files with embedded space(s) in them. Combinations of the path and file name must be less than 256 characters.
- The default location for searching for certain files (i.e. “Session,” “Option,” “Data,” “Plot,” and “Output” files) is now the last location (folder) to which the user saved that type of file or from which he accessed that type of file. There is a separate “memory” for file location for each of the above-listed file types.

- Improvements have been made to the “Export to Excel” feature associated with the “Summary Report” of a session run. . This feature allows the user to select which variables will be exported to Excel by checking/un-checking, in the “Export to Excel” column, the boxes corresponding to the variable rows the user wishes to export. The plots are exported as well, in a separate Excel “Plots” sheet.
- Additional session and option files have been added to the “SessionFiles” and “OptionFiles” folders. These folders contain sample sessions that allow the user to quickly run a specific set of models and model options for a selected dataset.
- The dichotomous Weibull model can accept a lower bound on power specified by the user. The EPA default choice (power restricted to be greater than or equal to 1) can still be checked, but if the user wishes not to restrict the power in that way, s/he may specify a value greater than or equal to zero; zero was the only other option in previous versions and that could cause biologically unrealistic fitted curves and numerical problems.
- The Toxicodiffusion model no longer needs the R(D)com Active-X control and will run with any version of R, 2.6.2 or later.
- Plots created by BMDS can be viewed using capabilities within BMDS or using GnuPlot. Those two options are accessed under the “Tools” menu item, the “View Plot” option. Using GnuPlot, the user can edit the plots to choose colors, fonts, line styles, etc.
- The option screen for the ten Berge CxT (concentration-time) model BMDS 2.1.2 had been improved to—address some issues and to allow saving the output file with a name of the user’s choosing. More importantly, CxT results from the ten Berge model are automatically exported to an Excel template file containing two customizable plots, one that shows the contour of concentration and time combinations for a user-specified probability and a second that shows the probability of response as a function of either concentration or time. In both plots, the user specifies the values of the other variables in the model.

Like BMDS 2.1.1, BMDS 2.1.2 contains the following additions/enhancements over BMDS 2.0:

- The ten Berge CxT model alluded to in item 5 above, allows for fitting of dichotomous response data sets having two or more explanatory variables (as in acute inhalation toxicity experiments). The explanatory variables can be entered as main effects or in interaction (cross-product) terms. The user can request the value (and its bounds) of one explanatory variable when a response rate is specified (fixing the other explanatory variables at some user-specified values) and/or conversely, the value (and its bounds) of the response rate, given specification of all explanatory variables.

- The executable for the set of models known as the exponential models, proposed by Dr. Wout Slob of RIVM in The Netherlands has been expanded to allow the assumption of log-normally distributed data (the previous versions of the exponential models and all other continuous models in BMDS assume that the data are normally distributed). The four exponential models fit by BMDS are defined and labeled as follows:

  Model 2: m(dose) = a*exp{sign*b*dose}

  Model 3: m(dose) = a*exp{sign*(b*dose)d}

  Model 4: m(dose) = a*(c—(c-1)*exp{-*b*dose})

  Model 5: m(dose) = a*(c—(c-1)*exp{-*(b*dose)d})

  where “sign” indicates the direction of change in the responses (sign=+1 for increasing responses; sign=-1 for decreasing responses).

- A version of a new ToxicoDiffusion model for continuous outcomes (Zhu et al., 2005) allows for the analysis of repeated-measures data. The BMDS Toxicodiffusion model is able to characterize toxic effects (e.g., neurotoxicity) that potentially evolve with time points by
  - Modeling a dose-response along a time-course of repeated response measurements;
  - Computing benchmark doses and their confidence limits along the time course.

  The ToxicoDiffusion model includes graphical outputs showing the observed and model-predicted time-course data, residuals, and a summary of the bootstrap-based BMDL calculations.

  For further detail see Zhu, Y., Jia, Z., Wang, W., Gift, J., Moser, V.C., and B.J. Pierre-Louis (2005), *Data Analysis of Neurobehavioral Screening Data: Benchmark Dose Estimation. Regulatory Toxicology and Pharmacology*, pp 190–201.

BMDS 2.2 (BUILD 66)

September 6, 2011—EPA is now distributing the final release of Version 2.2 (Build 66) of the Benchmark Dose Software (BMDS). Key enhancements in BMDS 2.2 (Build 66) include:

- **Multiple Tumor Analysis—**BMDS 2.2 adds the capability to perform a combined analysis of multiple tumors. If the user is willing to assume that those tumors are independent and are well described by a multistage-cancer model, then the Multiple Tumor Analysis capability (accessed through the

File/New or File/Open tool-bar choices) allows the user to estimate BMDs and BMDLs for the combined incidence of the tumors in question (i.e., BMDs and BMDLs for the likelihood of getting one or more of those tumors).

- **Trend Test for Dichotomous Data—**Another major addition is the new capability to perform a trend test on dichotomous data sets. This is the first in a series of trend test to be added to BMDS (future versions will also include trend test for continuous and nested data). The trend testing feature can be found on the dataset screens, accessible once a dataset has been identified by the user as containing dichotomous response data. The test performed is the Cochran-Armitage trend test described by Haseman (1984).
- **The Dichotomous Hill model has been modified—**Changes to the parameter initialization section of the Dichotomous Hill code have improved the convergence features of this model.
- **Automatic Transfer of Variable Name Changes to Other Option Files in a Session—**When working within a session, variable name changes (e.g., for dose, sample size, response, mean, or standard deviation variables) made in one option file (i.e., for one model) can be “transferred” to other option files included in that session (i.e., those for other models). The user will be prompted to determine if variable name assignment changes made in one option file should be made in all other option files included in that session. Thus, users can change variable name assignments once in a session, without having to make those changes separately in every option file.
- **Default Column Headers for New Datasets—**Note also that newly created dichotomous, continuous or nested model data files will start with default column headers, in a particular order, as appropriate for the type of data (e.g., Dose, N, and Effect for dichotomous datasets; Dose, N, Mean, and Std for summarized continuous datasets). The user may change those default headers, but will be warned that doing so may affect the running of BMDS-supplied sessions that look for those default names.

BMDS 2.2 (BUILD 67)

December 8, 2011—EPA is now distributing BMDS 2.2 (Build 67), which include minor modifications to the user interface.

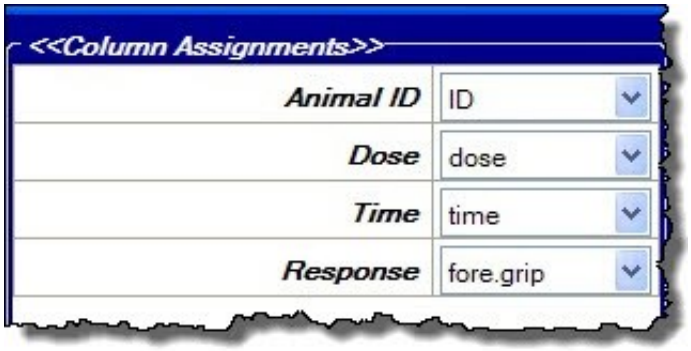
BMDS 2.3 (BUILD 68)

September 12, 2012—BMDS 2.3 introduces more flexible error-trapping functionality, enabling users to store essential comments, documentation, notations, etc. on their data in the datasets and spreadsheets without triggering a data validation error.

Previously, BMDS ran validation checks on the dataset each time the file was opened. BMDS would interpret notes, comments, extraneous text, etc. contained in the dataset as data errors and would not open the file. This would require opening the file in a separate program and purging any comments or text.

In BMDS 2.3, the application instead checks for data errors when the data is sent to the model. BMDS bases its validation on the dataset's column assignments from the Option Screen.

After you open the dataset, select the Model and Model Type, and then select **Proceed**, the Option Screen displays. In the Column Assignments section of the Option Screen, specify the data labels corresponding to the dataset variables (see the following screenshot).



When you click **Run**, BMDS will validate and error-check the data for only those assigned columns. BMDS will then display a message box describing any errors related to invalid values or blank cells found in those columns.

BMDS will also flag any duplicate column headers if they conflict with the Column Assignments specifications. Note that BMDS is case-sensitive, so BMDS considers dose, Dose, and DOSE to be separate variable names.

BMDS 2.3 also features the following fixes and enhancements:

- Fixes a problem reported by users of Microsoft Office in Windows 7, in which clipboard errors would crash both BMDS and Microsoft Office.
- Warns the user when saving a file using a name that exceeds the Windows limit of 256 characters. To correct the problem, rename the file or move the file to a directory higher in the hierarchy.
- Enhances Option screen validation to provide more thorough parameter constraint checking and to display pop-up messages describing errors.
- Fixes bug that prevented BMDS from adding a new/existing data set to the Session Grid.
- Fixes bug related to dynamically drawn dialog boxes.

- An issue was discovered in the computation of the A3 model log-likelihood for the continuous models when the user specified the variance parameter alpha. While this issue is being investigated and resolved, the option to specify alpha has been disabled for those models.
- Fixes intermittent bug where occasionally, when running the exponential model, BMDS failed to display a summary graph and report, even when output files were produced.
- Edits and updates to several Help topics:
  - Updated all Model Description topics to reflect upper parameter limit of 18 for some models.
  - Added the following topics under “Other Data or Analysis Types”: Data With Negative Means, Test for Combining Two Data Sets for the Same Endpoint
  - Added the following Troubleshooting topics: Help File Does Not Display, Decimal Separator Should Be a Period (see Section 3, “Usage Tips,” in this file for more information)
  - Added description of multitumor model (.d) file to the Multiple Tumor Analysis topic.
  - Added text to the Dichotomous Hill and Logistic models descriptions to address occasional error messages that appear for these models.
  - Under the “Graphic Output from Models” topic, added the subtopic “Error Bar Calculations,” explaining how BMDS generates error bars for various model types.

BMDS 2.3.1 (BUILD 69)

September 28, 2012—BMDS maintenance release Version 2.3.1 (Build 69) replaces Version 2.3 (Build 68). It simplifies how data validation errors for certain models are reported to the user. BMDS 2.3 also introduced user interface improvements.

None of the actual dose-response models in BMDS were modified for versions 2.3 and 2.3.1.

BMDS 2.4 (BUILD 70)

BMDS 2.4 includes several enhancements to improve usability and ensure accurate and reliable results, such as more informative plot titles and the ability to change an option file on the fly within a session. The help file includes a new

section on “BMDS Best Practices” containing valuable information and guidance on such topics as optimization criteria, alternative models, re-initializing parameters, and lognormal response option, among others.

Also, in this release, the BMDS install package includes ICF International's BMDS Wizard, an Excel-based tool that facilitates the preparation and organization of, and enhances the reporting capabilities of, BMDS modeling sessions.

BMDS 2.4 adds the following new or enhanced functionality:

- BMDS plots now provide more informative titles, such as “Weibull Model, with BMR of 10% Extra Risk and 0.95 Lower Confidence Limit for the BMD (BMDL).”
- BMDS now includes the cancer slope factor for the MS_Combo output.
- When an option file is modified via the Session Grid and saved under a new name, BMDS now automatically links that file to the current session.
- In a modeling session, after changes are made to a model option file, BMDS lists the changes for the user and asks whether they should be applied to the other model option files in the session. A warning is given to remind the user that changes to option files will affect other sessions that use those option files.

BMDS 2.4 also features the following fixes or changes:

- Gnuplot files now remain on the screen until the user closes them.
- Fixes a problem where exporting rows to Excel would shift column values to different headers on the Dichotomous Format and Continuous Format worksheets.
- Fixes a problem where BMDS dichotomous models treated “%Positive” as Incidence data.
- Fixes a problem where cut and paste operations on session data fields worked erratically on Windows 7 systems.
- Fixes a problem where BMDS could not open datasets saved with a capital .DAX extension.
- Fixes a problem where selecting a column in the data grid for a Log10 transformation returned incorrect results.
- Removes “Exact” as an available solution in the exponential model for summary data.
- Removes the “Extra” option for all continuous models but Hill.
- Removes the Optimization section from the options screens for all models that are not affected by optimization settings.

- Changes the default model iterations for all models from 250 to 500.
- Harmonizes the output for all continuous models so that when the “Rel Dev.” BMR type is selected in the option screen, the “Risk Type” reported in the output file says “Relative deviation” rather than “Relative risk.”
- Fixes a problem in the Multitumor Model (ms_combo) where BMDS failed to return a valid combined BMDL if the largest dose in the first dataset listed in the tumor analysis was less than the maximum dose in the other tumor analysis datasets.
- Edits and updates several Help topics, including:
  - A new section, “BMDS Best Practices for Obtaining Optimal Model Convergence.”
  - A new topic under Troubleshooting: “Avoid using special characters in filenames.”
  - A new topic documenting the model files (with their version numbers) used in BMDS 2.4.
  - A new appendix for BMDS version history information that originally appeared in those versions' readme files.
  - A new note on log transformations for the topic “Data Transformation Types.”

ICF INTERNATIONAL'S BMDS WIZARD

The BMDS 2.4 install package includes ICF International's BMDS Wizard, an Excel-based tool that facilitates the preparation and organization of and enhances the reporting capabilities of BMDS modeling sessions. This install includes multiple copies of the ICF BMDS Wizard files that are preformatted for continuous, dichotomous, and dichotomous-cancer datasets.

BMDS “power users” employ ICF BMDS Wizard as a shell to simplify the BMD modeling process by streamlining data entry, model selection, option file development, output file reporting, and model comparisons.

ICF BMDS Wizard 1.7 can also export Microsoft Word-formatted reports that employ the latest EPA-approved reporting format (as of February 15, 2013). It can only export reports for continuous, dichotomous, and dichotomous-cancer models.

To run the ICF BMDS Wizard, go to the BMDS 2.4 program directory and locate the “BMDS Wizard 1.7” subdirectory. ICF has included a readme and quickstart guide to the software. Please refer to that documentation for details on running the tool.

More information on the ICF BMDS Wizard can be found at ICF's Web site.

Please note that ICF BMDS Wizard is not endorsed or approved by EPA. Please contact ICF International at wizard@icfi.com for support.

BMDS 2.5 (BUILD 82)

BMDS 2.5 provides updates to ICF International's BMDS Wizard, which includes support for 32-bit and 64-bit versions of Microsoft Office on Windows 7, as well as a new MS_Combo (multi-tumor) template.

In addition, BMDS 2.5 contains various improvements to model stability and reliability.

RESOLVED ISSUES

BMDS 2.5 features the following enhancement and fixes:

- The BMDS Tools>View Plot menu entry has been simplified to make it easier to generate a plot from a previously created .plt file.
- The Multistage, Multistage Cancer and MS_Combo models now provide accurate results when non-integer input data values for Incidence and Number of Subjects used.
- The Multistage, Multistage Cancer and MS_Combo models now work correctly when beta parameters are specified by the user. Previously, the models would fail to calculate BMDL.
- The Power model now honors the direction of adversity specified by the user. Previously, the model always determined the direction automatically.
- An intermittent crash in the MS_Combo model has been resolved.
- Several Help topics have been revised, including:
- Specified in the Troubleshooting section that path+filenames should not exceed 127 characters.
- Added a topic documenting the MS_Combo model input file.
- Added Appendix B, which documents, for each model options screen, all of that screen's fields, including any field constraints.
- Updated the following topics to reflect BMDS .out files content: Continuous Model Text Output, Continuous Model Maximum Likelihood, Tests of Fit.

BMDS 2.6

BMDS 2.6 includes several enhancements to improve usability and ensure accurate and reliable results.

BMDS 2.6 also introduces a significant new feature: the ability for BMDS to automatically detect and, optionally, install software updates. This feature will ensure BMDS users have access to the latest version of the software with up-to-date fixes and enhancements.

The BMDS install package includes ICF International's BMDS Wizard, an Excel-based tool that facilitates the preparation and organization of, and enhances the reporting capabilities of, BMDS modeling sessions. See the next section on the ICF BMDS Wizard for more information.

BMDS 2.6 features the following enhancement and fixes:

- Resolved the following issues related to the nested models (NLogistic, NCTR, and Rai and van Ryzin):
  - The approach to evaluating goodness-of-fit for the nested models has been changed. Now, a bootstrap-based approach (using the fitted model and the underlying beta-binomial distribution of the observations) is used to evaluate the lack of fit. This obviates the need to group the litter-specific observations across litters and avoids asymptotic approximations.
  - Fixed a calculation error that occurred when the litter-size covariate (LSC) was larger than the litter size. (Although the reliability of the Rai and van Ryzin model has been improved, there is a remaining issue where the model erroneously reports the same value for the BMD and BMDL under certain circumstances.)
  - Added scaled residual of interest calculations to the results report. Output includes min, average, and max scaled residual of interest, and number of litters used for the calculation.
- BMDS now handles file and path names more robustly across all models. Specific changes include:
  - Full path length (folder plus file name) is now 255 characters rather than 127.
  - Spaces and ampersands (&) are now permitted.
  - Fixed several issues that occurred when the user specified output and session names in some models.
  - BMDS now supports UNC (network) path names structured as *\\ComputerName\ShareName\Path* (e.g., *\\FileSrv1\Users\JDoe\USEPA\BMDS260*). The total number of characters cannot exceed 255.

- The ToxicoDiffusion and MS_Combo models are now out of “beta” status. Detailed technical documentation of these models can be viewed or downloaded from the BMDS Download page.
- The ToxicoDiffusion model can now run when R has been installed on a per-user basis.
- Resolved an issue with the Linear and Polynomial models where incorrect MLE's were produced for non-constant variance in some situations.
- Resolved an issue so that BMDS now correctly calculates and displays Standard Error Estimates for all models in the “Parameter Estimates” table, whereas previously most models displayed “*”.
- Changed the color scheme for BMDS plots so they are easier to read.
- Included the most recent version of gnuplot (version 4.6.3).
- Fixed the Export to Excel function so it can export results for sessions containing any number of models. (Previously, sessions containing more than 24 models produced an error during export.)
- Fixed an issue so that BMDS now supports regional settings for the decimal separator in the user interface and in spreadsheets created by the Export to Excel function. However:
  - Files generated by BMDS (such as the .out files and .d files) will still show “.” as the decimal.
  - No “thousands separator” (regardless of regional setting) can be used in the data; that is, one thousand can only be written as 1000 rather than as 1,000.
- Added the following items to the summary table in the BMDS user interface: “Scaled Residual for Control Group” and “Scaled Residual for Dose Group Nearest the BMD”. The relevant values are already printed out in the “Goodness of Fit” table.
- Improved the e-Ticket system for users to request support and guidance. The new URL is http://bmds.epa.gov/eticket.
- Fixed an issue in the Power model where the specified power parameter output value was displayed incorrectly in the output text.
- Fixed an error in the restricted linear model when variance is non-constant.
- Fixed the alpha parameter initialization feature in the model options screen.
- New data grid windows now default to display 1000 rows. The previous default was 100.
- In addition to minor changes to accommodate the fixes and enhancements described above, the following Help file topics have been significantly revised or added:

- Added: Troubleshooting>No Thousands Separator Can Be Used in the Data
- Added: Troubleshooting>Requesting Support using eTicket
- Added: Using BMDS 2.6.0>Keeping BMDS Up to Date
- Added: Model Descriptions>Multitumor (MS_Combo) Model Description
- Added a note to the Output From Models>Text Output from Models>Dichotomous Model Text Output topic, describing how standard error methods are calculated for parameters for multistage models vs. other dichotomous models. Also added text to the Continuous Model Text Output and Nested Model Text Output topics describing how their parameter standard errors are obtained.
- Revised text on standard error calculations for the continuous model topics.
- Updated the Model Descriptions>Nested Model Descriptions topic to describe how the goodness-of-fit p-values are calculated using a bootstrap approach. The Nested Model Description subtopics also include revised formula descriptions.
- Updated the topic “Models Included in BMDS 2.6.0” to reflect updated versioning information.
- Updated several topics in “Appendix A: Model Input File Format Descriptions” to reflect user interface changes. Also added input file details for the Dichotomous Hill and Quantal with Background Dose models.
- Updated several topics in “Appendix B: Model Options Screen Fields Reference” to reflect user interface changes.

BMDS 2.6.0.1

BMDS 2.6.0.1 contains the following fixes and enhancements:

- Resolves an issue in BMDS 2.6 that prevented users from specifying parameter values for Continuous models. (BMDS still prevents users from specifying the Continuous model Alpha parameter to work around an open issue where BMDS sometimes reports a non-optimal A3 log likelihood when the Alpha parameter is specified.)
- Resolves an issue with previous versions where BMDS occasionally reported incorrect scaled residuals when a session referenced multiple data files with differing dose values.

- Enhances the Nested models' text results to display the minimum, maximum, and mean of the absolute value of the scaled residuals, as well as the minimum, maximum, and mean of the scaled residuals.
- Resolves an issue where BMDS 2.6 could not display plots generated by previous BMDS versions.
- Implements a fix for an intermittent issue where the BMDS Wizard did not import plots generated by BMDS 2.4 and later.
- Correctly validates the v parameter for the Continuous Hill model, an issue since BMDS 2.3. Although the v parameter must be $0 < v \leq 1$ for Dichotomous Hill, it should be unconstrained for the Continuous Hill model.
- Adds an Update button to the About BMDS box (accessible from the Help>About menu item). Click the Update button to have BMDS check for and optionally install a BMDS update.