

May 29, 2009

REVISED DRAFT

**IMULTISTAGE WEIBULL TIME-TO-TUMOR MODEL
IN EPA'S BENCHMARK DOSE SOFTWARE (BMDS)**

TESTING DOCUMENT

**BATTELLE
505 King Avenue
Columbus, OH 43201-2693**

**EPA Contract Number EP-C-05-030
Work Assignment 3-17**

Prepared for

**John Fox, Work Assignment Manager
National Center for Environmental Assessment
Office of Research and Development
U.S. ENVIRONMENTAL PROTECTION AGENCY
Washington, DC 20460**

**Marla Smith, Project Officer
Engineering and Analysis Division
Office of Science and Technology
Office of Water
U.S. ENVIRONMENTAL PROTECTION AGENCY
Washington, DC 20460**

EPA Disclaimer

The material in this document has not been subject to Agency technical and policy review. Views expressed by the authors are their own and do not necessarily reflect those of the U.S. Environmental Protection Agency. Mention of trade names, products, or services does not convey, and should not be interpreted as conveying, official EPA approval, endorsement, or recommendation. Do not quote or cite this document.

Battelle Disclaimer

This report is an interim work prepared for the United States Government by Battelle and is for discussion purposes only. In no event shall either the United States Government or Battelle have any responsibility or liability for any consequences of any use, misuse, inability to use, or reliance upon the information contained herein, nor does either warrant or otherwise represent in any way the accuracy, adequacy, efficacy, or applicability of the contents hereof.

Table of Contents

	<u>Page</u>
1.0 INTRODUCTION AND OBJECTIVES	1
1.1. Intended Audience	2
1.2. Module Development and Testing Issues	2
1.3. Test Datasets	3
2.0 COMPONENT CONSISTENCY TESTS	4
2.1. Utilities.....	5
2.2. Input	5
2.3. Processing	6
2.4. Function Evaluations	7
2.5. Gradient and Hessian Evaluations	8
2.6. Results of Component Consistency Tests.....	9
3.0 SYSTEM PERFORMANCE TESTS	9
3.1. Testing with Fixed t_0	10
3.2. Testing with Estimated t_0	12
3.3. Maximum Likelihood Estimates of Parameters and Benchmark Dose (BMD) ...	13
3.4. Benchmark Dose Profile Likelihood Confidence Interval.....	14
3.4.1. Difficulties in Evaluating the Profile Log-Likelihood Function.....	14
3.4.2. The Impact on Efficiency.....	15
3.4.3. The Impact on Stability.....	16
3.4.4. The Impact on Accuracy	16
3.5. Results of Performance Tests.....	17
3.6. Effect of Donlp3 - Silent Mode parameter setting on parameter estimates	17
Appendix A Detailed Listing from Fitting Multistage Weibull Models to Test Datasets Using BMDS and TOXRISK (Parameter t_0 Fixed).....	A1
Appendix B Detailed Listing from Fitting Multistage Weibull Models to Test Datasets Using BMDS (Parameter t_0 Estimated).....	B1

MULTISTAGE WEIBULL TIME-TO-TUMOR MODEL IN EPA'S BENCHMARK DOSE SOFTWARE (BMDS)

TESTING DOCUMENT

1.0 INTRODUCTION AND OBJECTIVES

A time-to-tumor (or, equivalently, time-to-event) model describes the probability of a test subject exhibiting some health-related event, such as death from tumor or tumor onset, by a specified observation time t when the subject is exposed to a toxin at a given dosage rate d . EPA's Benchmark Dose Modeling Software (BMDS) includes a module to fit a time-to-tumor model to dose-response data using a multistage Weibull model form. For some positive integer k , the general k -stage Weibull model is described by the following statistical (cumulative) distribution function

$$F(t, d, t_0, c, \beta_0, \beta_1, \dots, \beta_k) = \begin{cases} 1 - \exp\left\{ - (t - t_0)^c \sum_{i=0}^k \beta_i d^i \right\} & \text{if } t > t_0 \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

where $c, t_0, \beta_0, \beta_1, \dots, \beta_k$ are model parameters.

This document presents the approach and outcome of validation and verification efforts associated with the development of the module within BMDS for fitting a multistage Weibull time-to-tumor model. These efforts included system tests to check for consistency and stability and performance tests to assess model estimates generated by the module relative to those reported by an established standard. This document is one of a series of documents that details the development and use of the multistage Weibull time-to-tumor model within BMDS. The other documents in this series include:

- "Multistage Weibull Time-to-Tumor Model in EPA's Benchmark Dose Software (BMDS): Methodology Description," which details the algorithms and statistical methodology used to fit the model, estimate model parameters and the benchmark dose (BMD), and calculate profile likelihood confidence intervals.
- "Multistage Weibull Time-to-Tumor Model in EPA's Benchmark Dose Software (BMDS): Basic User Installation and Guide," which describes the installation process, the command line execution of the module, and the format of the input and output files for this module.
- "Multistage Weibull Time-to-Tumor Model in EPA's Benchmark Dose Software (BMDS): Source Code Installation and Description," which provides details on how to compile and install the source code for this model.

1.1. Intended Audience

This document is written for users who wish to review and verify the functionality of the BMDS multistage Weibull time-to-tumor module and to evaluate its performance. To ensure a sufficient understanding and benefit from the contents of this document, the reader should have familiarity with the following:

1. Intermediate to advanced knowledge of C programming.
2. Basic knowledge of Makefile scripting.
3. Intermediate knowledge of Microsoft Windows XP. Familiarity with the use of the command shell and the modification of internal settings.
4. Intermediate knowledge of BMDS. Familiarity with the general format of .(d) input files and .out output files.
5. Intermediate knowledge of statistics. Familiarity with the multistage Weibull model, as described in the Methodology Description document.

To install the BMDS multistage Weibull module, please consult the Basic User Installation and Guide. For specific details on the module's source code, please consult the Source Code Installation and Description document.

1.2. Module Development and Testing Issues

The module addressed within this document provides a multistage Weibull time-to-tumor modeling capability to BMDS. At this time, only model parameter estimation with asymptotic standard errors and correlation matrix, and BMD estimation with profile likelihood confidence interval, are active in the module. Other features, such as an analysis of deviance table and slope estimation, require further development and testing and may be activated in future releases.

The current release of the BMDS multistage Weibull time-to-tumor module, Version 1.5, was compiled using gcc-3.4.2. All development and testing was performed using Microsoft Windows XP Service Pack (SP) 2. Because testing and code refinements continued as this testing document was completed, it is possible that the module may produce different outcomes than those reported in this document when applied to the same input datasets.

The testing carried out on the module can be divided into two distinct categories:

- *Component consistency tests*, presented in Section 2.0, were used to check individual components of the code to ensure they function correctly. These checks are built into the source code and can be activated using compiler options.
- *System performance tests*, presented in Section 3.0, were used to compare the output produced by the module to an established standard. For those test cases where the value of the parameter t_0 in equation (1) was considered fixed (e.g., at zero), output generated

by the existing statistical software package TOXRISK¹ was used as the standard for comparison. A software package that executes standard types of health risk assessments, TOXRISK fits a multistage Weibull model to time-to-tumor data, then estimates BMD from the fitted model and calculates its profile-likelihood confidence interval². For test cases in which the parameter t_0 was treated as unknown and needed to be estimated, only simulated data from the multistage Weibull model were used, and the original simulation model was used as the standard for comparison.

In the course of developing various modules within BMDS, EPA has encountered certain issues when implementing an approach to calculating confidence intervals for the slope of the dose-response curve at a user-specified dose. These same issues were also encountered in developing the multistage Weibull time-to-tumor module for BMDS. They include:

- Instability in the code across different versions of the MinGW *gcc* compiler, due to slight differences in numerical precision.
- Boundary violations raised by the public domain optimization software *donlp3*, which prompts the objective function to return an improper value (e.g., negative infinity) and prevents the optimization process from completing successfully. This problem can occur during the calculation of the profile likelihood confidence interval for the benchmark dose (see Section 3.4)

Further details on these issues are included in the document, “Development and Testing Report on Two Software Modules That Use the Profile Likelihood Method for Computing Confidence Intervals on the Slope of a Dose-Response Curve Within Benchmark Dose Modeling Software (BMDS),” which is available from EPA.

1.3. Test Datasets

Three datasets containing actual bioassay data were used as input to the tests presented in this document. They were derived from the results of laboratory experiments in which a group of subjects were exposed to different dosage levels of a given toxin, and the presence, or lack, of a tumor in the subjects at a given point in time were recorded. The three experiments (with associated shorthand labels) were:

- Nasal squamous cell carcinoma (hcho5);
- Female mice alveolar/bronchiolar aden/carc (fm_alvbr); and
- Female mice hemangiosarcomas (fm_hemang).

¹ Toxicological Risk Assessment Program (1995). Developed by K. Crump, R. Howe, C. Van Landingham and W. Fuller, Clement International Corporation, Ruston, LA under contract to Electric Power Research Institute, Palo Alto, CA

² Crump, K. S. (1995). Calculation of benchmark doses from continuous data. *Risk Analysis*, **15**, 79–89.

In addition, two simulated datasets were also used in testing which EPA generated using a function written in the statistical software package S. This function simulated tumor onset data (and death for fatal tumor models) from the multistage Weibull time-to-tumor model in equation (1) with specified values for the model parameters. Times of death from unrelated causes (i.e., representing censored data or a competing risk distribution) were simulated independently, also from a user-specified multistage Weibull model with $t_0 = 0$. The two simulated datasets, and associated details on the simulation, are as follows:

- Simulated Test Dataset #1 (sim11jun07a):
 - The experimental design of the simulated dataset involved:
 - 4 dose levels: 0.00, 0.75, 2.50, 7.50
 - 50 subjects per dose level
 - Experiment duration of 104 (weeks)
 - The data were simulated using:
 - Tumor response from a 1-stage Weibull model for fatal tumors with parameters $c = 4.86$, $t_0 = 23$, $\beta_0 = 1.03\text{E-}011$, and $\beta_1 = 1.54\text{E-}010$
 - Censoring from a 1-stage Weibull model with parameters $c = 2$, $\beta_0 = 1.00\text{E-}004$, and $\beta_1 = 1.00\text{E-}008$.
- Simulated Test Dataset #2 (sim11jun07a):
 - The experimental design of the simulated dataset involved:
 - 4 dose levels: 0, 75, 250, 750
 - 50 subjects per dose level
 - Experiment duration of 104 (weeks)
 - The data were simulated using:
 - Tumor response from a 1-stage Weibull model for fatal tumors with parameters $c = 5$, $t_0 = 23$, $\beta_0 = 1.07\text{E-}010$, and $\beta_1 = 2.53\text{E-}013$.
 - Censoring from a 1-stage Weibull model with parameters $c = 2$, $\beta_0 = 1.00\text{E-}015$, and $\beta_1 = 1.00\text{E-}018$

2.0 COMPONENT CONSISTENCY TESTS

As noted in the Source Code Installation and Description document, the program file `model.c` is at the center of the module's relationship structure, because it contains the `main()` function. However, when component consistency tests are executed on the module, it is necessary for a different set of source code (`test.c` instead of `model.c`) to be recompiled which uses a different `main()` function and a different set of compiler options. The primary differences between the executables used in component consistency tests and the standard module executable 'msw.exe' are as follows:

- The test executables use only limited parts of the complete source code.
- The test executables create additional output to the terminal, and in some cases create output text files.

To simplify the testing process, the Makefile has been set up to create separate executables for each type of system test. Each of Sections 2.1 through 2.5 addresses a specific type of system test which is performed by creating and executing a specific test executable file named ‘test_***.exe’, where *** denotes the reference name of the component being tested (given within each subsection). To create this test executable, type ‘mingw32-make test_***’ at the command line, replacing *** by the component’s reference name.

2.1. Utilities

In order to test the utilities used by the module, the executable ‘test_utils.exe’ was created and executed. The executable has no arguments. The output from running the test should be:

```
Warning(test_utils): 1. Test print() function

Sum = 55
Sum from function d_sum() = 5.5000000000000000E+001
Sum from function d_sum_pow() = 5.5000000000000000E+001
test.c:65

Warning(test_utils): Test print() function
test.c:69

ERROR(test_utils): Test error() function
```

This test uses the two summation functions `d_sum()` and `d_sum_pow()`, to sum the sequence of numbers 1,2,...,10. The standard output print function `print()`, which prints the filename, line number, and a message to the standard output, is called twice. The other standard output print function `error()` is called at the end. It performs the same action as `print()`, but it also terminates the program. Modifications to the file `test.c` can be made to carry out different variations on these simple tests.

2.2. Input

In order to test whether the module inputs the information in the batch file correctly, the executable ‘test_input.exe’ was created and executed. The executable has a single argument which corresponds to the name of a correctly specified `.(d)` batch input file. The test outputs every specified option in the batch input file, as well as the first and last record in the data. The following is an example of the output:

```
Model name = Multistage Weibull
Model type = 1
Degree of polynomial = 1
User note = Test input batch file 'mr_nasal_f'
Input file = mr_Nasal_il.(d)
Output file = mr_Nasal_il.out
Output append flag = 0
Input data type = 1
No. data elements = 56
Number of parameters = 4
```



```

Parm. 1 fixed = -9.999000E+003
Parm. 2 fixed = 0.000000E+000
Parm. 3 fixed = -9.999000E+003
Parm. 4 fixed = -9.999000E+003
Initial. flag = 1
Parm. 1 initial start = 4.707960E+000
Parm. 2 initial start = -9.999000E+003
Parm. 3 initial start = 6.719109E-012
Parm. 4 initial start = 1.903161E-009
BMD calc. flag = 1
BMR value = 5.000000E-001, BMR type = 1, BMD time = 1.700000E+001
BMD conf. int. calc. flag = 1
BMD searchgrid no. = 8, BMD conf. level = 9.500000E-001
Slope calc. flag = 1
Slope dose = 1.000000E+001, slope time = 1.800000E+001
Slope conf. int. calc. flag = 1
Slope searchgrid no. = 8, slope conf. level = 9.500000E-001

Dose variable name = DOSE
Response variable name = CLASS
Time variable name = TIME
No. subjects variable name = N_SUBJECTS
First data line = 0      C      77      1
Dose = 0.000000E+000, resp. = C, time = 7.700000E+001, n = 1
Last data line = 1.42    I      89      5
Dose = 1.420000E+000, resp. = I, time = 8.900000E+001, n = 5
No. lines read = 56

```

The printed values can be compared to the contents of the batch input file as a check for consistency.

2.3. Processing

In order to test whether the inputs from the batch file are processed correctly, the executable ‘test_process.exe’ was created and executed. The executable has a single argument which corresponds to the name of a correctly specified .(d) batch input file. The test outputs the following information:

- Number of free parameters in the model
- Maximum dose
- First and last records in the data after sorting, listing the dose (Dose), response (resp.), observation time (time), and number of subjects (n).
- Number of dosage groups
- First and last records in the data summarized by dosage group, listing the dose (Dose), the location of the first group member in the sorted data (loc), the number of records, i.e., data lines in the group (n_data), and the total number of fatal (n_F) and incidental (n_I) tumors in the group.
- Number of dosage-by-response groups
- First and last records in the data summarized by dosage-by-response group, listing the dose (Dose) and response (resp.), the location of the first group member in the sorted data (loc), the number of records, i.e., data lines in the group (n_data), and the total number of subjects (n_sbjct) in the group.

- Minimum observation time.

The following is an example of the output from this test:

```
No. free parameters = 3

No. of free parameters = 3
Maximum dose = 1.420000
Sorted data, first element
Dose = 0.000000, resp. = C, time = 77.000000, n = 1

Sorted data, last element
Dose = 1.420000, resp. = I, time = 89.000000, n = 5

No. dosage groups = 3

Dosage group, first element
Dose = 0.000000, loc = 0, n = 12, n_F = 0, n_I = 1

Dosage group, last element
Dose = 1.420000, loc = 27, n = 29, n_F = 0, n_I = 21

No. dosage-response groups = 6

Dosage-response group, first element
Dose = 0.000000, resp. = C, loc. = 0, n_data = 11, n_sbjct = 49

Dosage-response group, last element
Dose = 1.420000, resp. = I, loc. = 35, n_data = 21, n_sbjct = 41

Minimum observation time = 43.000000
```

The output can be checked by directly examining the data (if the number of records is manageably small), or by carrying out the same calculations independently (if the number of records is large) using software such as Microsoft Excel.

2.4. Function Evaluations

In order to test whether the various analytically-defined functions in the module are specified correctly, the executable 'test_l.exe' was created and executed. A single argument to the executable includes the name of a correctly specified .(d) batch input file and user-specified starting values. The test outputs the following information:

1. The values of the multistage Weibull and GEV log-likelihood functions, at the user-specified starting parameter values. If both log-likelihoods are specified correctly in the source code, the function values should be nearly identical.
2. The value of the BMD defining function (if the BMD calculation option is specified), at the user-specified starting parameter values. Various components of the defining function, as well as type of benchmark response (BMR, noted as an indicator of either extra (i.e., relative) risk or added (i.e., additional) risk) are printed above the value of the defining function.

3. The value of all non-linear constraint functions for maximum likelihood estimation of the model parameters at the user-specified starting parameter values.
4. The value of all non-linear constraint functions for calculating the BMD profile log-likelihood (if the BMD calculation option is specified) at the user-specified starting parameter values. The output will include reprints of both items 2. and 3. above.

The following is an example of the output from this test:

```
Weibull log-likelihood = -4.2511656576443691E+001
GEV Log-likelihood = -4.2511656576443691E+001

d_gev_bmd(): (1 + gamma * (t_BMD - mu)) ^ (1 / gamma)=4.2192432358391761E+002
d_gev_bmd(): sum(b_i * BMD ^ i) [i = 1, nstage]=1.3999588646260322E-005
d_gev_bmd(): BMR type = 1
BMD equation at (BMD = 5.0000000000000000E+000) = -1.6288337646365124E-003

MLE likelihood non-linear constraints:
    Function 0 = 1.7954387976359953E-016

BMD profile likelihood non-linear constraints:
    Function 0 = 1.7954387976359953E-016

d_gev_bmd(): (1 + gamma * (t_BMD - mu)) ^ (1 / gamma)=4.2192432358391761E+002
d_gev_bmd(): sum(b_i * BMD ^ i) [i = 1, nstage]=1.3999588646260322E-005
d_gev_bmd(): BMR type = 1
    Function 1 = 0.0000000000000000E+000
```

The executable also creates text files, `gev_l.txt` and `msw_l.txt`, which contain the contribution of each record to the multistage GEV and Weibull log-likelihoods, respectively. The text output can be compared with the same calculations created independently using software such as Microsoft Excel. An example Excel file for this purpose, `Consistency_Check_Example.exe`, is provided with the code. Note that numerical errors (e.g. rounding) may cause some deterioration in the consistency, especially at high values of the dose.

2.5. Gradient and Hessian Evaluations

In order to test whether the various analytically-defined gradient and Hessian functions in the module are specified correctly, the executable ‘`test_lgrad.exe`’ was created and executed. A single argument to the executable includes the name of a correctly specified `.(d)` batch input file and user-specified starting values. The test outputs the values of the following derivatives, as well as their associated finite difference approximations, evaluated at the user-specified starting parameter values:

1. Gradient and Hessian of the multistage Weibull log-likelihood.
2. Gradient of multistage GEV log-likelihood.
3. Gradient of parameter MLE non-linear constraint functions.
4. Gradient of BMD profile log-likelihood non-linear constraint functions.

If the analytical derivatives are specified correctly in the code, their values should match the finite difference approximations reasonably closely. The following is an example of the output from this test:

```
Weibull log-likelihood gradient:
  Parm 1 grad. = -1.7955727610E-004, fin. diff. = -1.7955722183E-004
  Parm 2 grad. = -1.6165822198E+005, fin. diff. = -1.6166550185E+005
  Parm 3 grad. = -2.0455082104E+004, fin. diff. = -2.0455054920E+004
Weibull log-likelihood Hessian:
  Parm[1,1] Hess. = -1.0833851541E+003, fin. = -1.0833848893E+003
  Parm[2,1] Hess. = -9.1720780349E+011, fin. = -9.1720804308E+011
  Parm[2,2] Hess. = -2.2211365800E+022, fin. = -2.2211366022E+022
  Parm[3,1] Hess. = -1.2364501121E+011, fin. = -1.2364499546E+011
  Parm[3,2] Hess. = -2.5918807254E+019, fin. = -2.5918807438E+019
  Parm[3,3] Hess. = -1.4422368630E+019, fin. = -1.4422368844E+019
GEV log-likelihood gradients:
  Parm 0 grad. = 1.7188324883E-003, fin. diff. = 1.7188326972E-003
  Parm 1 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 2 grad. = -1.0988237980E+002, fin. diff. = -1.0987834309E+002
  Parm 3 grad. = -1.3903735139E+001, fin. diff. = -1.3903752610E+001
MLE log-likelihood non-linear constraint gradients:
  Function 0:
  Parm 1 grad. = 2.2164887362E+001, fin. diff. = 2.2164887362E+001
  Parm 2 grad. = 1.0000000000E+000, fin. diff. = 1.0000000000E+000
  Parm 3 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 4 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
BMD profile likelihood non-linear constraint gradients:
  Function 0:
  Parm 1 grad. = 2.2164887362E+001, fin. diff. = 2.2164887362E+001
  Parm 2 grad. = 1.0000000000E+000, fin. diff. = 1.0000000000E+000
  Parm 3 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 4 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Function 1:
  Parm 1 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 2 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 3 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
  Parm 4 grad. = 0.0000000000E+000, fin. diff. = 0.0000000000E+000
```

Note, however, that in some cases, the finite difference approximation may not work properly and produce wildly divergent results, especially if any of the user-specified parameters are too close to the boundary of the function support.

2.6. Results of Component Consistency Tests

The component consistency tests described above have been applied using each of the test datasets described in Section 1.3 as input. To date, none of the test results have indicated any problems with the internal consistency of the C code for the BMDS multistage Weibull module.

3.0 SYSTEM PERFORMANCE TESTS

In the system performance tests, the performance of the BMDS multistage Weibull module is compared to a specified standard. Like the component consistency tests discussed in Section 2.0, the system performance tests require a different set of source code (test.c instead of model.c) to

be recompiled which uses a different `main()` function and a different set of compiler options. To simplify this process, the Makefile has been set up to create a separate executable for the system performance test named 'test_start.exe'. To create this executable, type 'mingw32-make test_start' at the command line. The primary differences between this executable and the standard module executable 'msw.exe' are as follows:

- The test executable sends additional output to the terminal and creates additional output text files.
- The test executable will run significantly slower due to the additional input/output requirements.

3.1. Testing with Fixed t_0

In system performance tests where the parameter t_0 within the multistage Weibull model was fixed at a user-specified value, the specified standard for comparison was output from the existing software package TOXRISK (Section 1.2). The comparison involves fitting a commonly-specified multistage Weibull model to the same input data set using both BMDS and TOXRISK and evaluating any differences in the reported output. Each of the three real test datasets and the two simulated test datasets specified in Section 1.3 were used as input to these system performance tests. When working with the three real datasets, t_0 was fixed at 0, whereas for the two simulated datasets, t_0 was fixed at some feasible positive values (i.e., a value less than the earliest fatal tumor context that existed within the dataset.) The complete listings that result from fitting all possible multistage Weibull models using both TOXRISK and the module developed for the BMDS are found in Appendix A.

Note that BMDS calculates BMD and reports the time within the same units as the reported data (i.e., mg/kg/day and weeks), whereas TOXRISK calculates BMD in ug/kg/day, and specifies the time in years. For all listed results in Appendix A, BMD is calculated by TOXRISK at various values of extra (i.e., relative) risk for a subject at two (and, in some cases, at one) years of age, which is equivalent to 104 (or 52) weeks in BMDS. Therefore, when comparing the BMD and profile likelihood confidence interval and in order to match the dose units of the equivalent TOXRISK results, the results from BMDS have been converted to units of ug/kg/day (i.e., multiplied by a factor of 1000).

Appendix A also contains plots of the numerically-evaluated BMD profile log-likelihood value for different values of extra risk. The plotted points represent the dose levels where the constrained optimization returns a diagnostic code signaling convergence, indicating that the BMDS software has successfully evaluated the profile log-likelihood. The vertical, dotted reference line in each plot provides the location of the estimated BMD, while the horizontal dotted reference line represents the threshold. Thus, the confidence bounds are determined at the two extremes that represent crossing points furthest away from the BMD where the profile log-likelihood function falls below the dotted horizontal line. Note that the dose values used in the plots have been rescaled (by a factor of 1000) to match the TOXRISK results.

Within each of the results in Appendix A associated with applying the test datasets to the BMDS multistage Weibull module, some performance-related issue was encountered. These issues, and the location within the appendix in which they are encountered (i.e., A1 through A5), include the following:

A1 Nasal squamous cell carcinoma data (hcho5)

- In the 2- to 4-stage models with low settings of extra risk, the BMD profile log-likelihood function reaches a plateau, then drops steeply as the dose approaches 0 (e.g., Section A1.1.3, Incidental Extra Risk = 1.0E-06 at 104 Weeks).

A2 Female Mice Alveolar/Bronchiolar Aden/Carc (fm_alvbr)

- The lower and upper confidence bounds of the BMD (i.e., BMDL and BMDU) show some discrepancies between TOXRISK and BMDS for the both the 2- and 1-stage models at 104 and 52 weeks (Sections A2.1.2 and A2.2.1.)
- In the 2-stage model with low settings of extra risk, the BMD profile log-likelihood function reaches a plateau, then drops steeply as the dose approaches 0 (e.g., Section A2.1.3, Incidental Extra Risk = 1.0E-06 at 104 weeks). The profile log-likelihood is also evaluated only once after the function drops steeply and falls below the threshold.
- In the 2-stage model with high settings of extra risk, the profile likelihood appears slightly discontinuous as the dose approaches 0 (e.g., Section A2.1.3, Incidental Extra Risk = 1.0E-01 at 104 weeks).
- In the 1-stage model the parameter estimates show some discrepancies between TOXRISK and BMDS (Section A2.2.1).
- In the 1-stage model with mid-range settings of extra risk, a noticeable but inconsistently occurring “bump” appears in the upper tail of the profile likelihood function (e.g., Section A2.2.3, Incidental Extra Risk = 1.0E-05 at 52 Weeks).

A3 Female Mice Hemangiosarcomas (fm_hemang)

- The lower and upper confidence bounds of BMD show some slight discrepancies between TOXRISK and BMDS at 104 weeks and more substantial discrepancies at 52 weeks for both the 2- and 1-stage models (Sections A3.1.2 and A3.2.2).
- In both the 2- and 1-stage models, a noticeable but inconsistently occurring “bump” appears in the upper tail of the profile likelihood function (e.g., Section A3.1.3, Incidental Extra Risk = 1.0E-06 at 104 Weeks). For the 1-stage model, a “bump” occurs on the lower tail of the profile likelihood function occurs for Incidental Extra Risk = 1.0E-04 at 52 weeks (Section A3.2.3).

A4 Simulated Dataset 1 (sim11jun07a)

- The confidence bounds of BMD are consistently narrower for TOXRISK than for BMDS at 104 weeks for the 3-, 2- and 1-stage models (Sections A4.1.2, A4.2.2, and A4.3.2).

A5 Simulated Dataset 2 (sim11jun07b)

- The confidence bounds of BMD are consistently narrower for TOXRISK than for BMDS at 104 weeks for the 3-, 2- and 1-stage models (Sections A4.4.2, A4.5.2, and A4.6.2).

These issues, and possible remedies, are explained in greater detail in Sections 3.3 and 3.4.

3.2. Testing with Estimated t_0

In test cases where the model parameter t_0 was not user-specified but instead was estimated from the data, results could not be compared between BMDS and TOXRISK because of an inconsistency in the implementation of the multistage Weibull model between the two software programs. Specifically, TOXRISK can produce a zero estimate for t_0 , whereas BMDS cannot. (Please consult Section 7.4 of the Methodology Description document for an explanation of this restriction in BMDS.) TOXRISK, for example, estimates t_0 as 0 when the 1-stage Weibull model is fit to Simulated Dataset #2 (sim11jun07b). Therefore, only the two simulated datasets were used in test cases in which t_0 was estimated. By doing so, the parameter estimates from BMDS were compared to the specified values of the parameters of the model which generated the simulated data. Unfortunately, this approach does not allow for evaluating the BMDS-calculated profile likelihood confidence intervals for BMD.

The detailed results of these tests are included in Appendix B. (For an explanation of the profile-likelihood plots, see Section 3.1.) The following is a summary of those results:

B1 Simulated Dataset 1 (sim11jun07a)

- Maximum likelihood estimation for the (over-parameterized) 3-stage Weibull model (Section B1.1.1) correctly identifies β_2 and β_3 as equal to zero, because the tumor response in the data is simulated by a 1-stage Weibull. While the estimates of c and t_0 are similar to the “true” parameter values of the simulation model in order of magnitude, the estimates of β_0 and β_1 deviate substantially from their “true” values. In fact, the estimate of β_0 is zero, which might be explained, at least in part, by the strong dose-response relationship relative to the baseline response in the simulation model (i.e., β_1 is an order of magnitude greater than β_0). Not surprisingly, therefore, the BMD estimates from the simulated data (Section B1.1.2) deviate substantially from the “true” values of the BMD as determined by the model used to generate the simulated data. All profile log-likelihood functions (Section B1.1.3) are unimodal and smooth.
- The 1-stage Weibull model produces the same parameter estimates (Section B1.2.1) as the 3-stage Weibull model (Section B1.1.1). Therefore, the same estimates of BMD are produced by the 1-stage Weibull (Section B1.2.2) as the 3-stage Weibull (Section B1.1.2). The confidence bounds for the BMDS, however, are narrower for the 1-stage Weibull than the 3-stage Weibull, most noticeably in the upper bound. This is to be expected, because an over-parameterized will tend to produce wider confidence intervals than a correctly parameterized model. The profile log-likelihood functions for the 1-stage Weibull (Section B1.1.3) are unimodal and smooth, but they

appear to have a slightly different shape from those of the 3-stage Weibull (Section B1.2.3). This difference may be due to the profile log-likelihoods for the 1-stage having a “sharper peak,” as evidenced by the differences in scales of the horizontal “Benchmark Dose” axis, and the fact that BMDS stops evaluating the profile log-likelihood once the function falls below a given distance from the threshold. (Currently, the distance is set at $4 \times [\text{maximum log-likelihood} - \text{threshold}]$).

B2 Simulated Dataset 2 (sim11jun07b)

- As with Simulated Dataset 1 (sim11jun07a), maximum likelihood estimation for the (over-parameterized) 3-stage Weibull model (Section B2.1.1) correctly identifies β_2 and β_3 as both equal to zero, estimates c and t_0 to be similar in magnitude to the “true” simulation model values, and produces very poor estimates of β_0 and β_1 . Consequently, the estimates of BMD (Section B2.1.2) do not agree with the “true” BMDs associated with the model that generated the simulated data. The profile log-likelihood functions (Section B2.1.3) are, again, unimodal and smooth.
- The 1-stage Weibull model produces the same parameter estimates (Section B2.2.1) and the same BMD estimates as the 3-stage Weibull model (Sections B2.1.1 and B2.1.2), but with narrower confidence bounds (Section B2.2.2). The profile likelihood functions for the 1-stage Weibull (Section B2.2.3) are similar, but they have a slightly “sharper peak” than those for the 3-stage model (Section B2.1.3).

The poor estimates for β_0 and β_1 and the problems encountered with BMD estimation seem to result from either the simulated datasets or the methodological theory, rather than the software implementation. (In fact, the parameter estimates of the 1-stage model for Simulated Dataset 1 (sim11jun07a) agree with estimates produced by TOXRISK. For the 1-stage model with Simulated Dataset 2 (sim11jun07a), TOXRISK estimates t_0 to be zero.) In particular, the presence of censored responses in the dataset and the use of maximum likelihood when t_0 is estimated affect the quality of parameter estimates. Section 7.0 of the Methodology Description document provides more detailed discussions on these topics.

3.3. Maximum Likelihood Estimates of Parameters and Benchmark Dose (BMD)

Calculations of model parameter and BMD estimates are generally very similar between TOXRISK and the multistage Weibull module created for BMDS. The only exception occurs when the shape parameter is estimated at the lower boundary of 1.0. This is seen in the example that fits a 1-stage Weibull model to data in fm_alvbr (Section A2.2 of Appendix A). In that case, the BMDS produces a model estimate with a slightly lower log-likelihood value than TOXRISK. This difference in the model parameter estimates also leads to slight differences in the estimates of the BMD. To solve this problem, the BMDS module may require some tuning adjustments to the numerical optimization for estimation of model parameters when the shape parameter is close to 1.0. Note, however, that a shape parameter estimate of less than 2.0 invalidates the asymptotic normality assumption, and therefore, could produce inaccurate standard error and profile likelihood estimates. Details are provided in the Methodology Description document.

3.4. Benchmark Dose Profile Likelihood Confidence Interval

Performance-related issues associated with calculating a profile likelihood confidence interval for the BMD within the BMDS multistage Weibull module are the result of difficulties in numerically calculating the profile log-likelihood function. These difficulties impact software performance in terms of efficiency (speed), stability, and accuracy. To date, attempts to resolve these difficulties have led to trade-offs between these three performance characteristics.

TOXRISK avoids some of these difficulties by replacing a nonlinear constraint in the optimization for calculating the profile log-likelihood function (i.e., the defining function, see Section 3.4.1) with a linear approximation. This may explain, at least partially, some of the observed differences in the profile likelihood confidence bounds between TOXRISK and BMDS.

3.4.1. Difficulties in Evaluating the Profile Log-Likelihood Function

Each time that the profile log-likelihood function is evaluated, BMDS is required to carry out a numerical optimization of a non-linear objective function with (at least) one non-linear constraint. In particular, as noted within the Methodology Description document, the objective function associated with the k -stage multistage Weibull time-to-tumor model is the log-likelihood of the multistage generalized extreme value (GEV) model, $l(\gamma, \mu, b_0, b_1, \dots, b_k)$, and the non-linear constraint is determined by the defining function of BMD for a given risk and time. For example, with extra (i.e., relative) risk equal to R at time t , the defining function for the BMD θ is

$$d(\theta, \gamma, \mu, b_0, b_1, \dots, b_k) = \sum_{i=1}^k b_i \theta^i + [1 + \gamma(t - \mu)]^{1/\gamma} \ln[1 - R]$$

The profile log-likelihood function, $l_p(\theta)$, is the maximum of the log-likelihood, with the defining function constrained at 0, i.e.,

$$l_p(\theta) = \max_{d(\theta, \gamma, \mu, b_0, b_1, \dots, b_k) = 0} l(\gamma, \mu, b_0, b_1, \dots, b_k)$$

In the unconstrained numerical optimization (i.e., maximum likelihood estimation of the model), a method to automatically scale the parameters was found, leading to substantial improvement in the stability of the optimization. The same automatic scaling of the parameters was used in the constrained optimization for the profile log-likelihood function. However, attempts to evaluate the profile log-likelihood with test data have shown that some additional scaling is required for the constrained optimization to converge. A scaling value $S > 0$ is required in the non-linear constraint, leading to the following alternate specification of the profile log-likelihood:

$$l_p(\theta) = \max_{S \times d(\theta, \gamma, \mu, b_0, b_1, \dots, b_k) = 0} l(\gamma, \mu, b_0, b_1, \dots, b_k)$$

Unlike the scaling for the parameters, a method that automatically (and reliably) scales the non-linear constraint has yet to be found. Some methods that have been tried, but have failed, to produce consistent results include:

- $S = (\text{constant}) \times (\text{defining function } d \text{ evaluated at the starting values})$
- $S = (\text{constant}) \times (\text{defining function } d \text{ evaluated at perturbed starting values})$

(Other approaches that apply more radical transformations of the constraint, such as taking the natural exponent of the defining function, have also proved unsuccessful.)

As a “brute-force” fix to this problem, the multistage Weibull module is set up to find an appropriate scaling value by using a search grid. Starting with a large value of the scaling value, the constrained optimization is repeatedly carried out while the scaling value is gradually decreased, until the optimization returns a diagnostic code signaling proper convergence.

An alternative, but related, method of starting with a very small scaling value and gradually increasing was not considered, because of concerns about accuracy. In particular, if the scale S is set to 0, the optimization would become unconstrained.

3.4.2. The Impact on Efficiency

The impact of using the “brute-force” scaling method on software efficiency is substantial. To calculate the upper and lower bound on the BMD profile likelihood confidence interval, the module executes an adaptive step search to find the location where the profile log-likelihood function dips below a threshold. A step search is used instead of, for example, an interval search, because it presents less of a problem in finding appropriate starting values for the constrained optimization. At each step, the optimum parameters found in the prior step are used as the starting values. If the optimization fails to converge, the software adaptively reduces the step size to try and obtain convergence.

An attempt was made to substantially improve efficiency by using a fixed value for S throughout the step search for the bounds. This would allow either the user to set S , or require the software to execute only a single brute-force search for S . This restriction, however, causes the adaptive step search to fail often. The suspected problem is that different values of S are required to evaluate the profile log-likelihood at different values of the dose.

As a compromise, the software is currently set up to carry out a search for S only if the constrained optimization returns a diagnostic code indicating convergence failure. Unfortunately, there is currently no definitive way to know whether a convergence failure has occurred due to poor choice of scaling value S , or due to a poor choice of starting values. Therefore, the software is forced to search a 2-dimensional grid of the scale value S and the step size, which can potentially result in a very large reduction in computational efficiency. Some of this reduction in efficiency may be mitigated by improving the order in which the search occurs over the 2-dimensional grid.

3.4.3. The Impact on Stability

Although improving numerical stability is the primary reason for using the brute-force method to find the scaling parameter S , the main trade-off is the reduction in numerical efficiency (as just noted). The practical evidence, however, suggests that the brute-force method is not sufficient for complete stability.

In Appendix A, plots of the numerically evaluated profile log-likelihood function show several cases where the function is evaluated just below the threshold, or appears to be discontinuous. This anomaly occurs at the lower extremes of the dose values where BMDS is searching for the location where profile log-likelihood falls below the threshold. For example, the profile log-likelihood plots in Section A2.1.3 {fm_alvbr, 2-stage, fixed $t_0 = 0$, incidental extra risk at 104 weeks} show cases of sudden cut-off in function evaluation and discontinuity at the lower dose values. These are possible symptoms of the software producing inaccurate values of the profile log-likelihood function near zero dose.

This erratic behavior of the profile log-likelihood raises some additional concerns about the optimization software *donlp3* used by the module. Many parts of the BMDS multistage Weibull module, including the brute-force scaling method, rely heavily on the accuracy of the convergence code. Further investigation is necessary to determine the extent, if any, to which the *donlp3* software may contribute to this problem, as well as to investigate how the optimization problem is specified analytically and/or numerically in the C source code.

3.4.4. The Impact on Accuracy

Assuming that the profile log-likelihood are accurately evaluated by the software, the numerical evidence from the test cases suggests that the profile log-likelihood function is not a consistently well-behaved unimodal function (i.e., having a single, moderately curved peak) that would lend itself easily to a root search for the upper and lower bounds. Plots of numerically evaluated profile log-likelihood functions are shown in Appendix A and Appendix B. An examination of the plots explains some of the difficulty in finding the confidence interval bounds.

In a number of test cases, the profile log-likelihood is non-unimodal. The profile log-likelihood plot in Section A3.1.3 {fm_hemang, 2-stage, fixed $t_0 = 0$, incidental extra risk at 104 weeks of $1.0E-06$ } illustrates the problem that results from a non-unimodal profile log-likelihood. At doses above the BMD (the vertical dotted line), the profile log-likelihood appears, at one point, to jump up and down below the threshold (the horizontal dotted line). The BMDS module tries to identify the furthest location from the estimated BMD at which the profile log-likelihood falls below the threshold, by continuing the step search for the crossing until the value of the profile log-likelihood is some distance below the threshold. (Currently, the distance is set at four times the distance between the unrestricted maximum log-likelihood and the threshold.) The software may need to be adjusted to allow the search to be widened in order to find locations that are farthest away from the BMD where the crossing occurs. Such a change, however, would come at a cost in terms of an increased number of times at which the profile log-likelihood is evaluated, leading to a substantial reduction in efficiency.

The profile log-likelihood function has also been observed to suddenly plummet below the threshold at lower dose values. A profile log-likelihood plot in Section A1.2.3 {hcho5, 3-stage, fixed $t_0 = 0$, incidental extra risk at 104 weeks of $1.0E-06$ } shows this sudden drop at lower dose values. This outcome creates substantial difficulty in the search for the precise location where the profile log-likelihood crosses below the threshold, because the function cannot be evaluated at any dose that is too far below the crossing point, i.e., beyond the ‘numerical domain’ of the profile log-likelihood. In particular, there is a substantial loss in efficiency as the software tries repeatedly and unsuccessfully to evaluate the profile log-likelihood function outside its ‘numerical domain’ during the search. A possible solution to this problem may be to rescale the profile log-likelihood function, such as using the logarithm of the translated dose.

3.5. Results of Performance Tests

The results of the performance tests suggest that further improvements, especially in the calculation of the BMD profile likelihood confidence interval, should be made within some components of the BMDS multistage Weibull module. The difficulty in evaluating the profile log-likelihood causes substantial inefficiencies. Using a Dell D630 laptop with a 2 GHz Intel Core 2 Duo processor, the BMDS module can take up to 1 minute to complete a single run of a test case using the standard module executable (msw.exe). Unfortunately, in order to gain stability, the loss in efficiency is a necessary trade-off. Significant effort will be required, and more potential difficulties will be faced, in trying to reduce the impact of this problem; in particular, finding a reliable automatic scaling method for scaling the non-linear constraint in the profile log-likelihood optimization is a process of trial-and-error that requires luck and persistence.

Note also, that some additional tests that have yet to be completed. They include testing the calculations for added (i.e., additional) risk and fatal risk (for the model where $t_0 > 0$).

3.6. Effect of *Donlp3* - Silent Mode parameter setting on parameter estimates

The optimizer *donlp3* used in calculating maximum likelihood estimates for the multistage Weibull model parameters generates diagnostic messages at different stages of the optimization process. The diagnostic messages are meant to help those users familiar with the operation of the *donlp3* code to identify the cause and location of potential issues with the optimization routines. The diagnostic messages are reported to the stdout (output terminal) and are controlled by the parameter DONLP_SILENT in the module “model.h.” Further description of the model.h module can be obtained from the source-code description document which is part of the MSW software module document set. The accepted values for the DONLP_SILENT parameter are 0 and 1. The diagnostic messages are suppressed when the optimizer is set to silent mode (DONLP_SILENT = 1) and is the default mode of operation for the software module. The silent mode should be turned off only when there are issues with the optimization results and a programmer needs to debug the code. This is due to the potentially large amount of diagnostic messages that could be displayed on the user screen. In an earlier version of the multistage

Weibull module, the silent mode was turned off. However, the current version of the MSW module (e.g., Version 1.5) operates with the silent mode on.

During the development of Version 1.5 of the MSW module, as the silent mode was turned on, results of unit testing determined that the DONLP_SILENT parameter setting appeared to affect the maximum likelihood estimates calculated by the *donlp3* optimizer. The *donlp3* optimizer routinely failed to achieve convergence with the DONLP_SILENT parameter set to 1. This *donlp3*-related issue has been identified, but any necessary modifications to the *donlp3* module will require extensive testing as this module is common to all the software modules within the BMDS package.

Example of MLE Parameter estimates with silent mode off (DONLP_SILENT = 0):

```
=====
Multistage Weibull Model. (Version: 1.5; Date: 05/31/2009)
Input Data File: .\Test Inputs\hcho5_1stage_auto.(d)
Gnuplot Plotting File:
                                     Fri May 29 11:29:18 2009
=====

Test input batch file with TOXRISK data 'hcho5.ttd'

~~~~~

The form of the probability function is:
P[response] = 1-EXP{-(t - t_0)^c *
              (beta_0+beta_1*dose^1)}

The parameter betas are restricted to be positive

Dependent variable = CLASS
Independent variables = DOSE, TIME

Total number of observations = 222
Total number of records with missing values = 0
Total number of parameters in model = 4
Total number of specified parameters = 1
Degree of polynomial = 1

User specifies the following parameters:
t_0      =      0

Maximum number of iterations = 64
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
c        =      6
t_0      =      0   Specified
beta_0   =      0
beta_1   = 1.29917e-014

Asymptotic Correlation Matrix of Parameter Estimates
( *** The model parameter(s) -t_0      -beta_0
      have been estimated at a boundary point, or have been specified by the user,
      and do not appear in the correlation matrix )

c          beta_1
```

c	1	-1
beta_1	-1	1

Parameter Estimates			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
c	7.05791	2.22176	2.70335	11.4125
beta_0	0	NA		
beta_1	9.88164e-017	1.0137e-015	-1.88801e-015	2.08564e-015

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table					
Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full Model	0	7			
Fitted Model	-118.539	4	0	3	<.0001
Reduced Model	0	3	0	4	<.0001
AIC:	241.078				

Data Summary						
CLASS						
	C	F	I	U	Total	Predicted Response
DOSE						
0	338	0	0	0	338	0
0.7	107	0	0	0	107	0
2	316	0	0	0	316	5
6	301	1	2	0	304	14
10	81	11	11	0	103	4

Minimum observation time for F tumor context = 79.3

Example of MLE Parameter estimates with silent mode on (DONLP SILENT = 1):

Message to the user screen - "8. Donlp Diagnosis: More than MAXIT iteration steps."

The MLE parameter estimates are the same as the Initial parameter estimates.

```
=====
Multistage Weibull Model. (Version: 1.5; Date: 05/31/2009)
Input Data File: .\Test Inputs\hcho5_1stage_auto.(d)
Gnuplot Plotting File:
Fri May 29 11:32:12 2009
=====

Test input batch file with TOXRISK data 'hcho5.ttd'

~~~~~

The form of the probability function is:
P[response] = 1-EXP{-(t - t_0)^c *
              (beta_0+beta_1*dose^1)}

The parameter betas are restricted to be positive
```

Dependent variable = CLASS
Independent variables = DOSE, TIME

Total number of observations = 222
Total number of records with missing values = 0
Total number of parameters in model = 4
Total number of specified parameters = 1
Degree of polynomial = 1

User specifies the following parameters:
t_0 = 0

Maximum number of iterations = 64
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
c = 6
t_0 = 0 Specified
beta_0 = 0
beta_1 = 1.29917e-014

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -t_0 -beta_0
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	c	beta_1
c	1	-1
beta_1	-1	1

Parameter Estimates			95.0% Wald Confidence Interval	
Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
c	6	1.94297	2.19184	9.80816
beta_0	0	NA		
beta_1	1.29917e-014	1.16368e-013	-2.15085e-013	2.41068e-013

NA - Indicates that this parameter has hit a
bound implied by some inequality constraint
and thus has no standard error.

Analysis of Deviance Table					
Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full Model	0	7			
Fitted Model	-118.79	4	0	3	<.0001
Reduced Model	0	3	0	4	<.0001
AIC:	241.58				

Data Summary						
CLASS						
	C	F	I	U	Total	Predicted Response
DOSE						
0	338	0	0	0	338	0
0.7	107	0	0	0	107	0
2	316	0	0	0	316	5
6	301	1	2	0	304	13
10	81	11	11	0	103	5

Minimum observation time for F tumor context = 79.3

Appendix A

Detailed Listing from Fitting Multistage Weibull Models to Test Datasets Using BMDS and TOXRISK (Parameter t_0 Fixed)

A1. Nasal squamous cell carcinoma data (hcho5)

A1.1. 4-Stage Model, Fixed $t_0 = 0$

A1.1.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-9.349809E+01	7.881766E+00	0	0.000000E+00
BMDS	-9.349809E+01	7.881766E+00	0	0.000000E+00

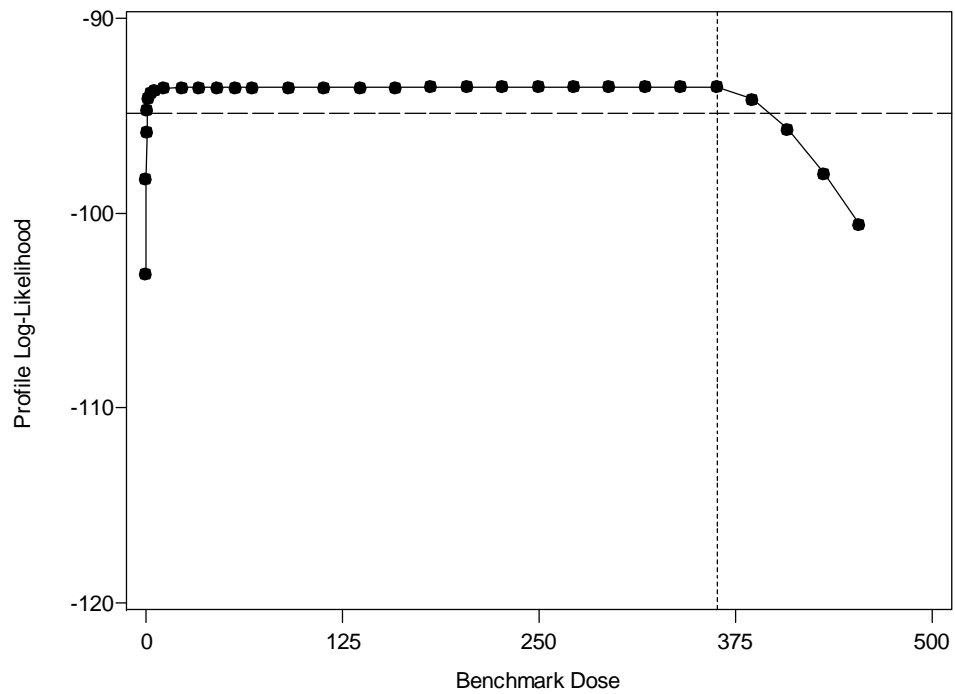
Software	Parameter MLE			
	β_1	β_2	β_3	β_4
TOXRISK	0.000000E+00	0.000000E+00	8.941701E-37	7.267803E-21
BMDS	0.000000E+00	0.000000E+00	0.000000E+00	7.267802E-21

A1.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

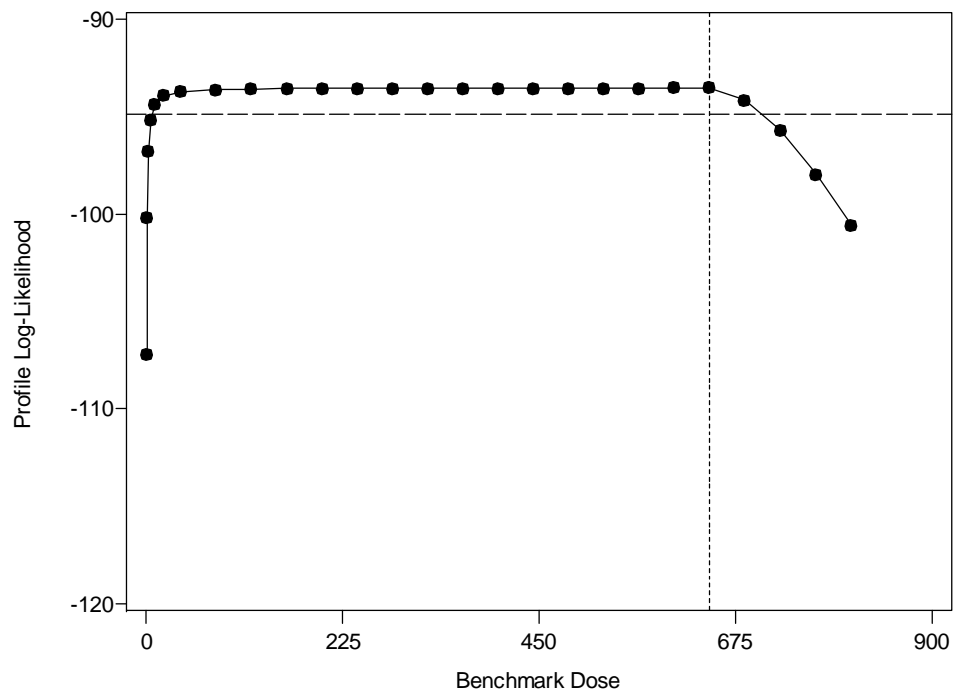
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	6.0463E-001	3.6325E+002	3.9781E+002
	BMDS	6.0463E-001	3.6325E+002	3.9781E+002
1.0E-05	TOXRISK	6.0464E+000	6.4596E+002	7.0743E+002
	BMDS	6.0137E+000	6.4596E+002	7.0743E+002
1.0E-04	TOXRISK	6.0466E+001	1.1487E+003	1.2580E+003
	BMDS	6.0466E+001	1.1487E+003	1.2580E+003
1.0E-03	TOXRISK	6.0059E+002	2.0429E+003	2.2374E+003
	BMDS	6.0059E+002	2.0429E+003	2.2373E+003
1.0E-02	TOXRISK	3.0579E+003	3.6370E+003	3.9831E+003
	BMDS	3.0579E+003	3.6370E+003	3.9831E+003
1.0E-01	TOXRISK	6.0284E+003	6.5444E+003	7.1672E+003
	BMDS	6.0288E+003	6.5444E+003	7.1672E+003

A1.1.3. Plots of Profile Log-Likelihood Functions

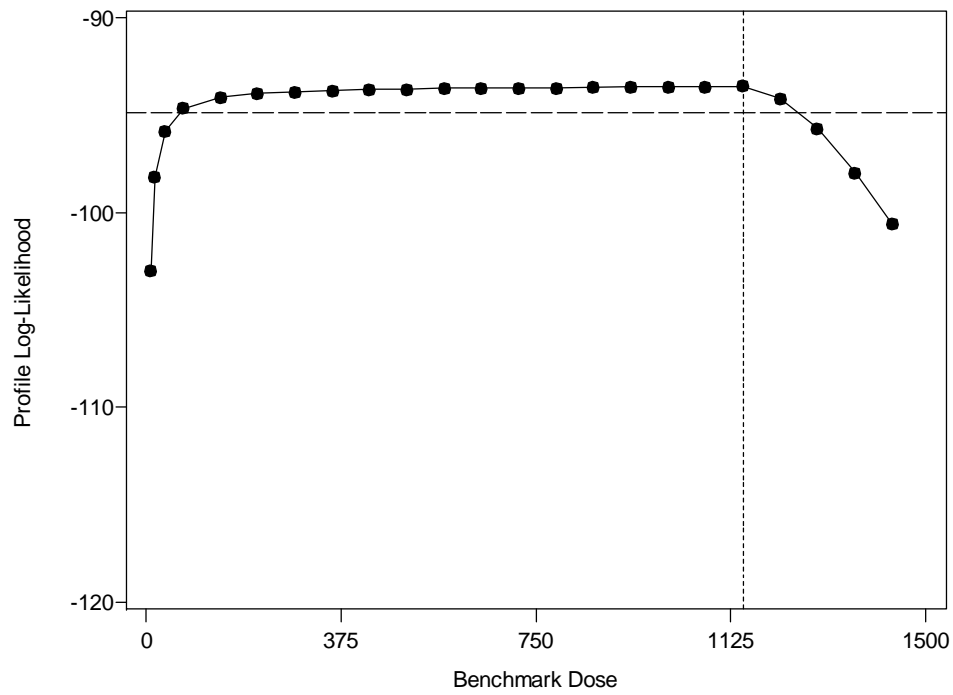
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



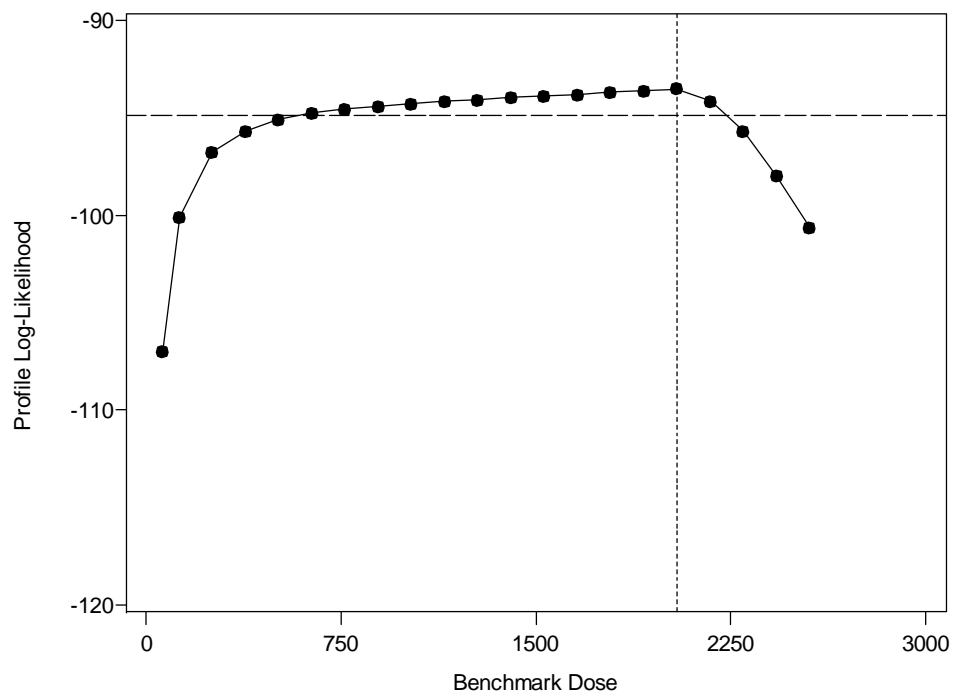
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



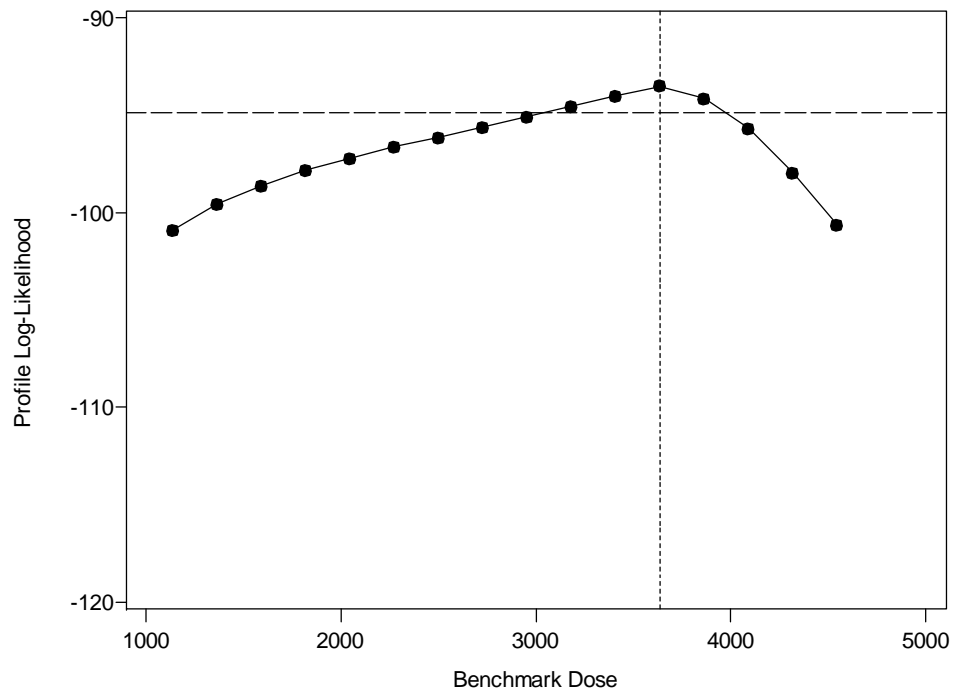
Incidental Extra Risk = $1.0\text{E-}04$ at 104 Weeks



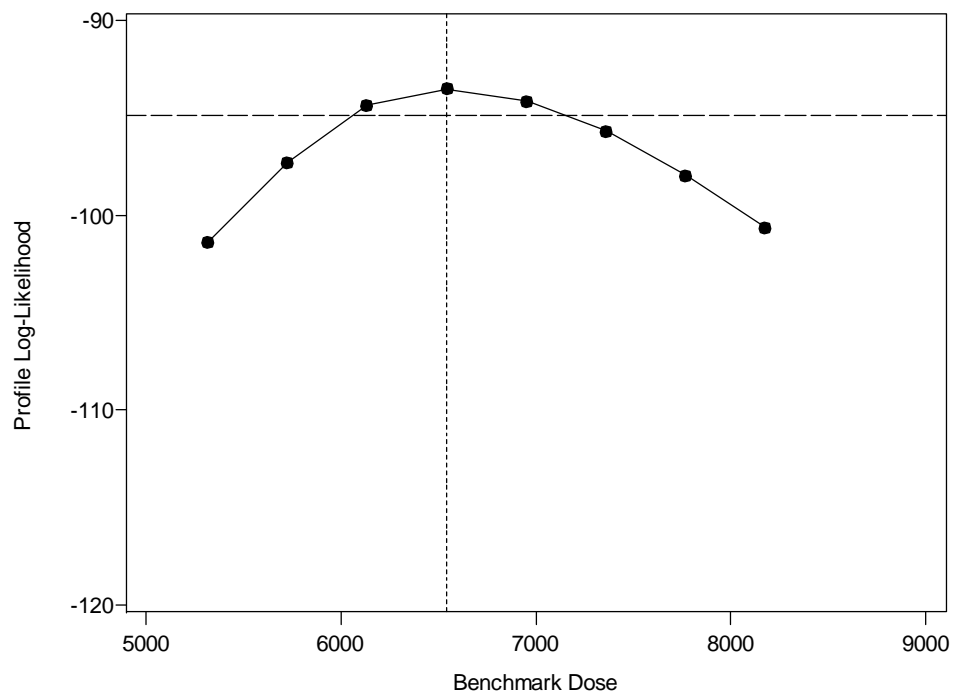
Incidental Extra Risk = $1.0\text{E-}03$ at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A1.2. 3-Stage Model, Fixed $t_0 = 0$

A1.2.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-9.854511E+01	7.618550E+00	0	0.000000E+00
BMDS	-9.854511E+01	7.618550E+00	0	0.000000E+00

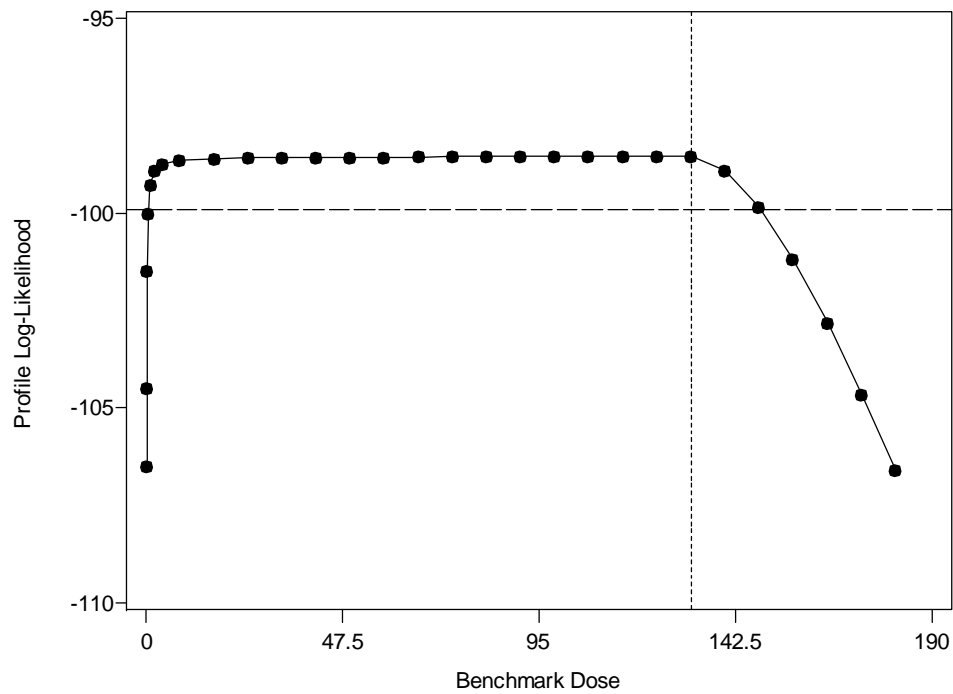
Software	Parameter MLE		
	β_1	β_2	β_3
TOXRISK	0.000000E+00	0.000000E+00	1.875848E-19
BMDS	0.000000E+00	0.000000E+00	1.875847E-19

A1.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

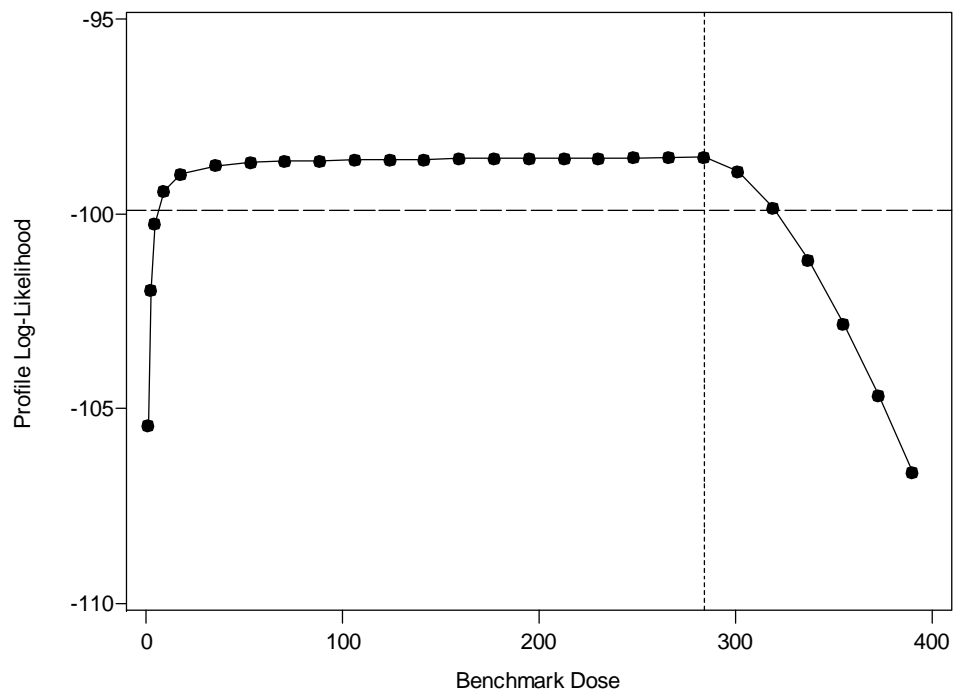
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	5.5717E-001	1.3182E+002	1.4867E+002
	BMDS	5.5717E-001	1.3182E+002	1.4867E+002
1.0E-05	TOXRISK	5.5717E+000	2.8400E+002	3.2030E+002
	BMDS	5.5717E+000	2.8400E+002	3.2030E+002
1.0E-04	TOXRISK	5.5680E+001	6.1186E+002	6.9008E+002
	BMDS	5.5680E+001	6.1186E+002	6.9008E+002
1.0E-03	TOXRISK	5.2403E+002	1.3184E+003	1.4870E+003
	BMDS	5.2403E+002	1.3184E+003	1.4870E+003
1.0E-02	TOXRISK	2.3693E+003	2.8447E+003	3.2084E+003
	BMDS	2.3693E+003	2.8447E+003	3.2084E+003
1.0E-01	TOXRISK	5.5855E+003	6.2259E+003	7.0219E+003
	BMDS	5.5855E+003	6.2259E+003	7.0219E+003

A1.2.3. Plots of Profile Log-Likelihood Functions

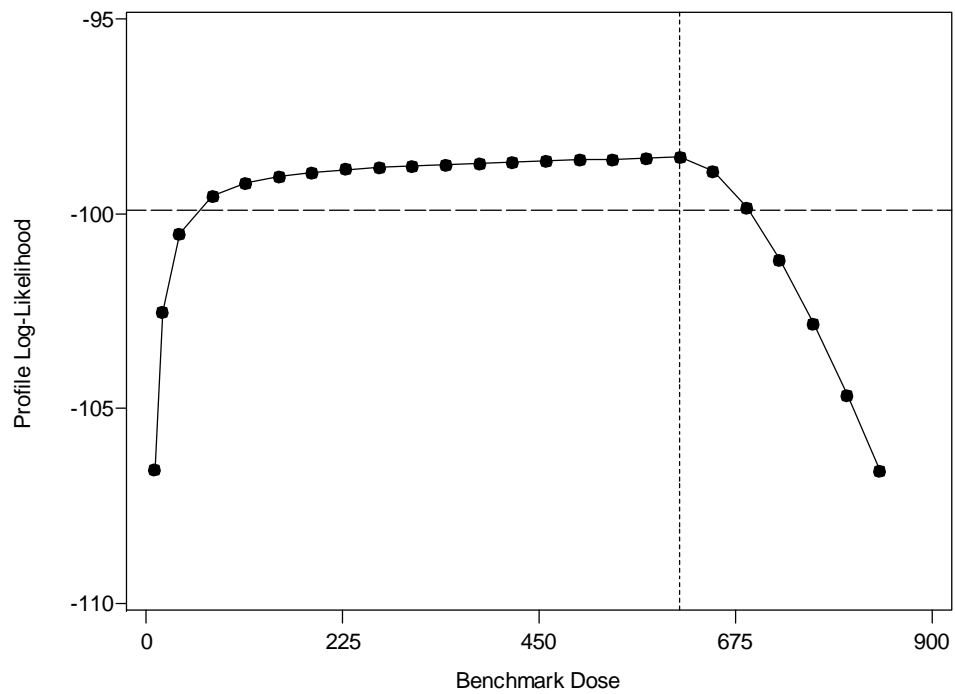
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



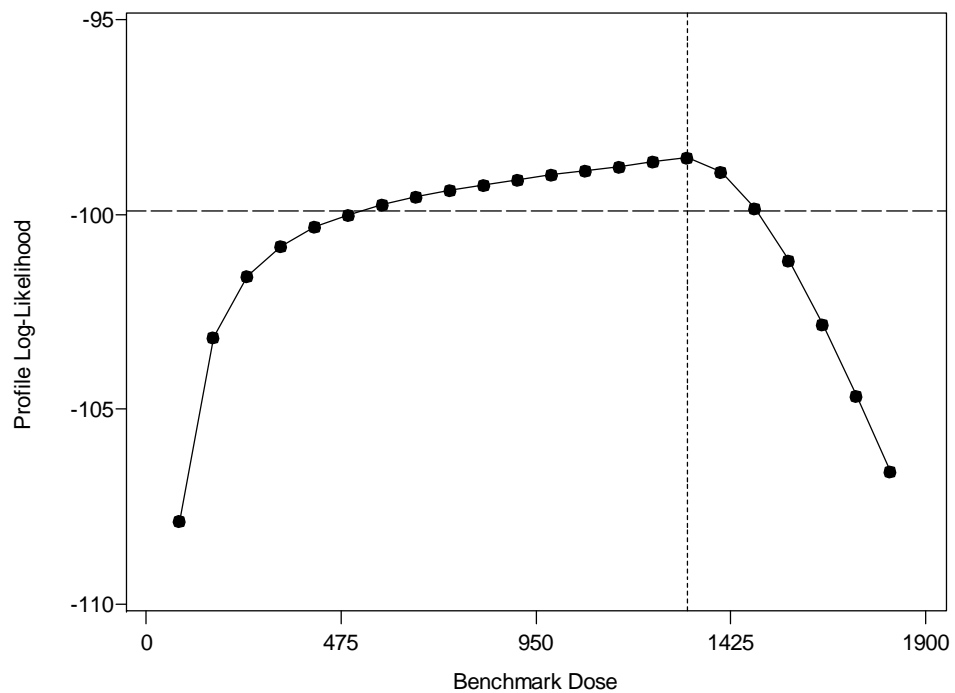
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



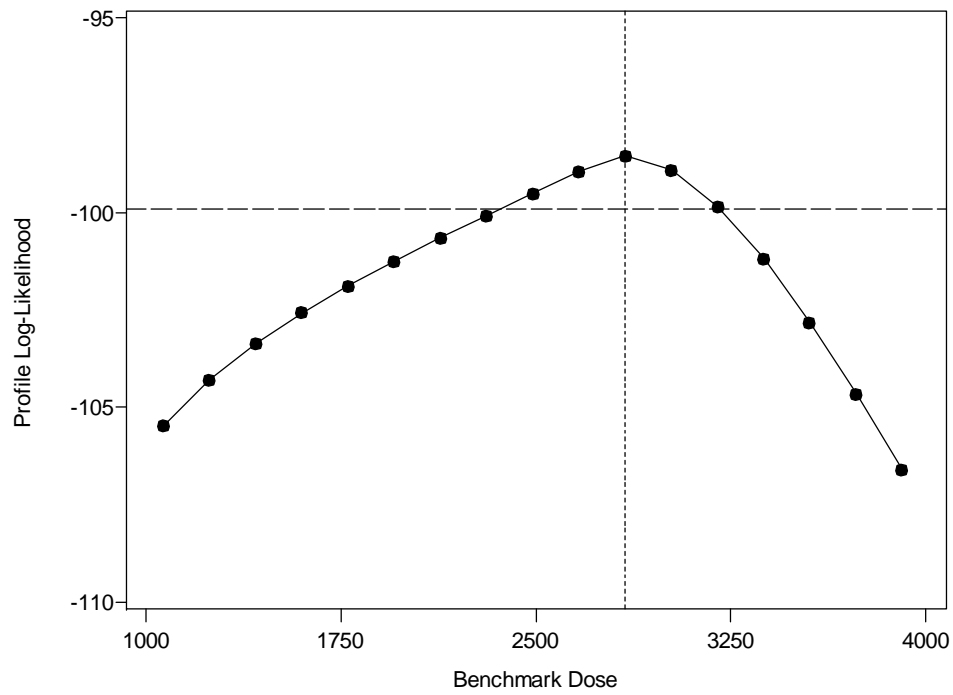
Incidental Extra Risk = 1.0E-04 at 104 Weeks



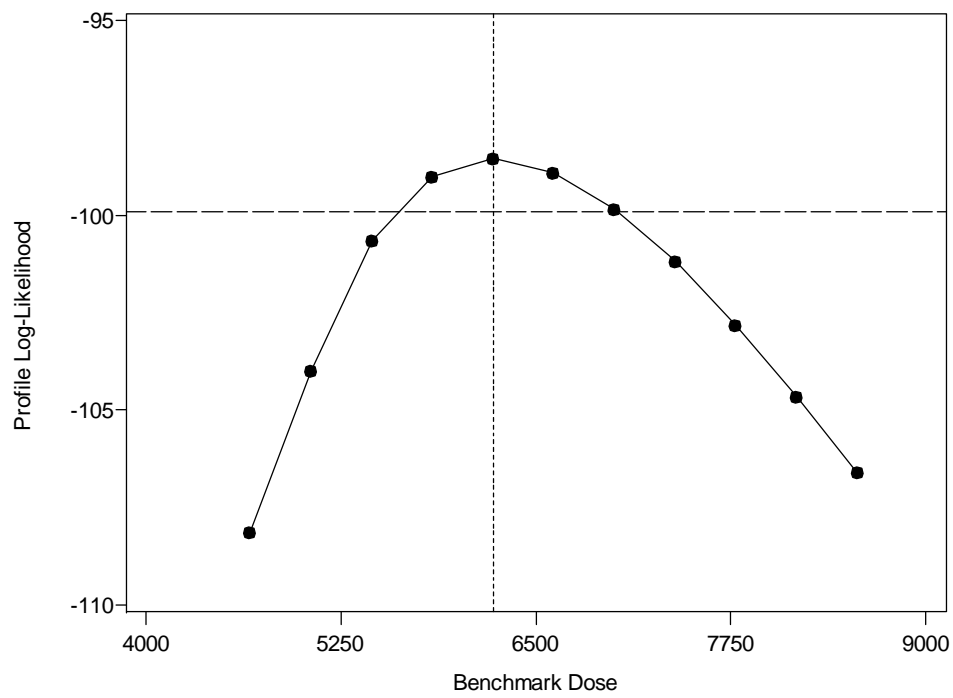
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A1.3. 2-Stage Model, Fixed $t_0 = 0$

A1.3.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-1.062194E+02	7.342179E+00	0	0.000000E+00
BMDs	-1.062194E+02	7.342173E+00	0	0.000000E+00

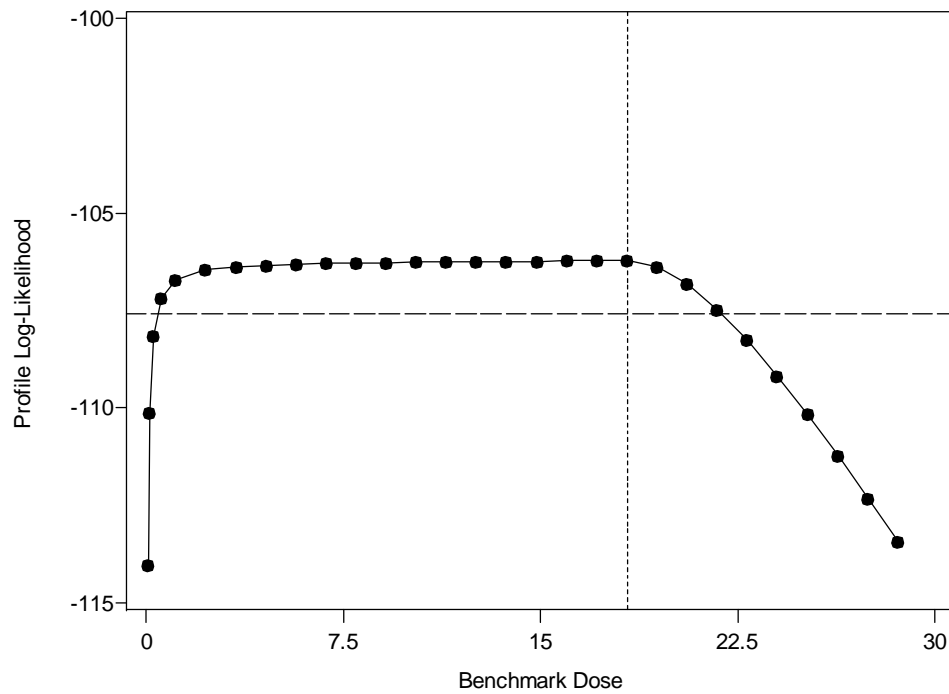
Software	Parameter MLE	
	β_1	β_2
TOXRISK	0.000000E+00	4.636361E-18
BMDs	0.000000E+00	4.636492E-18

A1.3.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

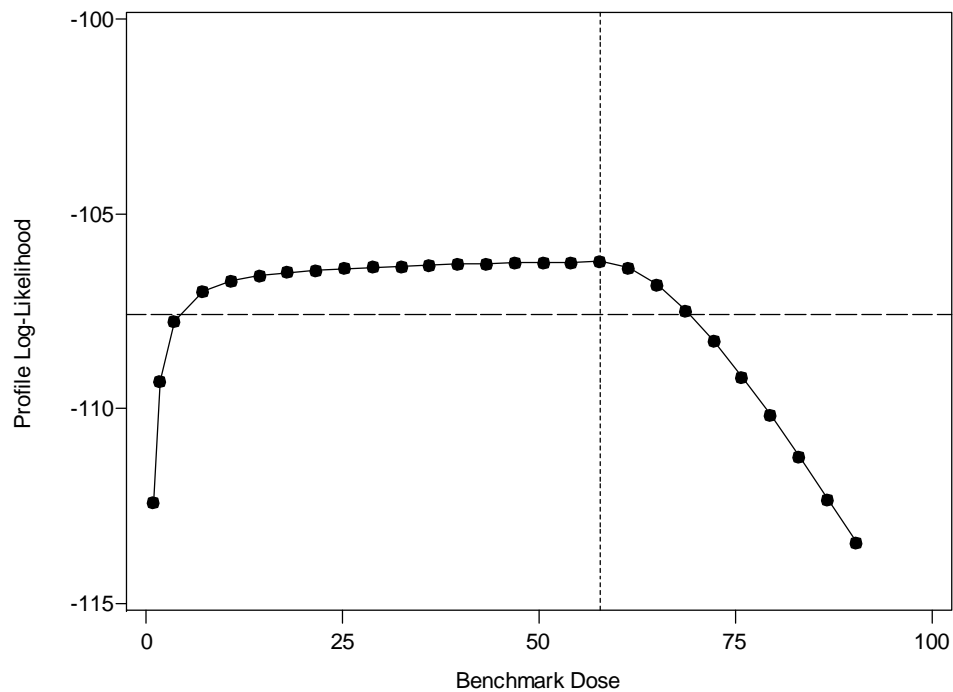
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	4.0982E-001	1.8289E+001	2.1879E+001
	BMDs	4.0982E-001	1.8289E+001	2.1879E+001
1.0E-05	TOXRISK	4.0814E+000	5.7837E+001	6.9189E+001
	BMDs	4.0814E+000	5.7837E+001	6.9189E+001
1.0E-04	TOXRISK	3.9272E+001	1.8290E+002	2.1880E+002
	BMDs	3.9272E+001	1.8290E+002	2.1880E+002
1.0E-03	TOXRISK	3.0480E+002	5.7851E+002	6.9206E+002
	BMDs	3.0480E+002	5.7851E+002	6.9206E+002
1.0E-02	TOXRISK	1.4806E+003	1.8335E+003	2.1934E+003
	BMDs	1.4806E+003	1.8335E+003	2.1934E+003
1.0E-01	TOXRISK	5.0514E+003	5.9366E+003	7.1019E+003
	BMDs	5.0514E+003	5.9366E+003	7.1019E+003

A1.3.3. Plots of Profile Log-Likelihood Functions

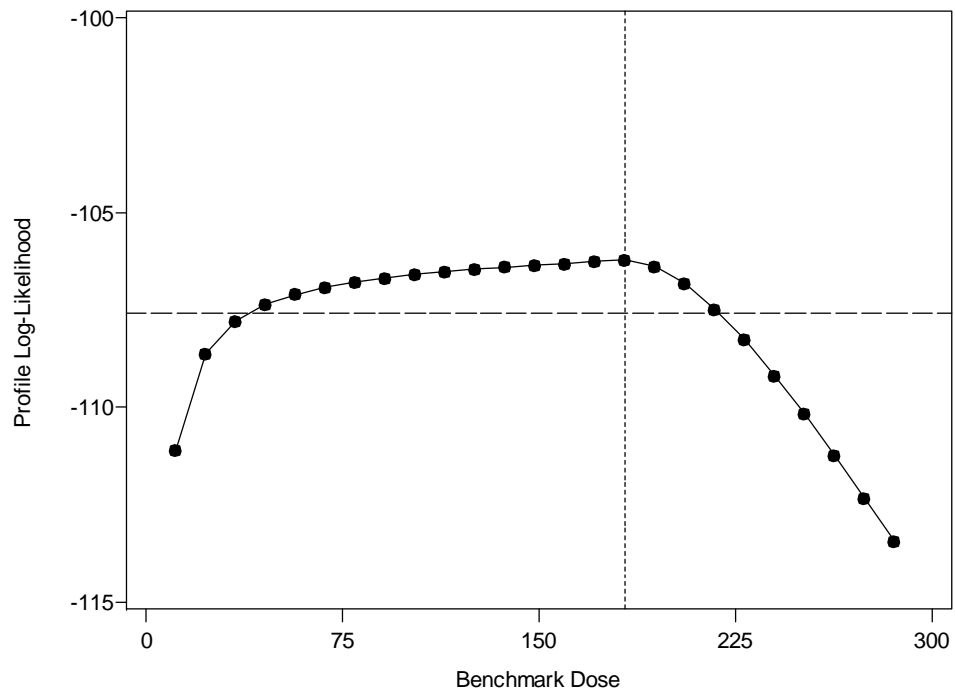
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



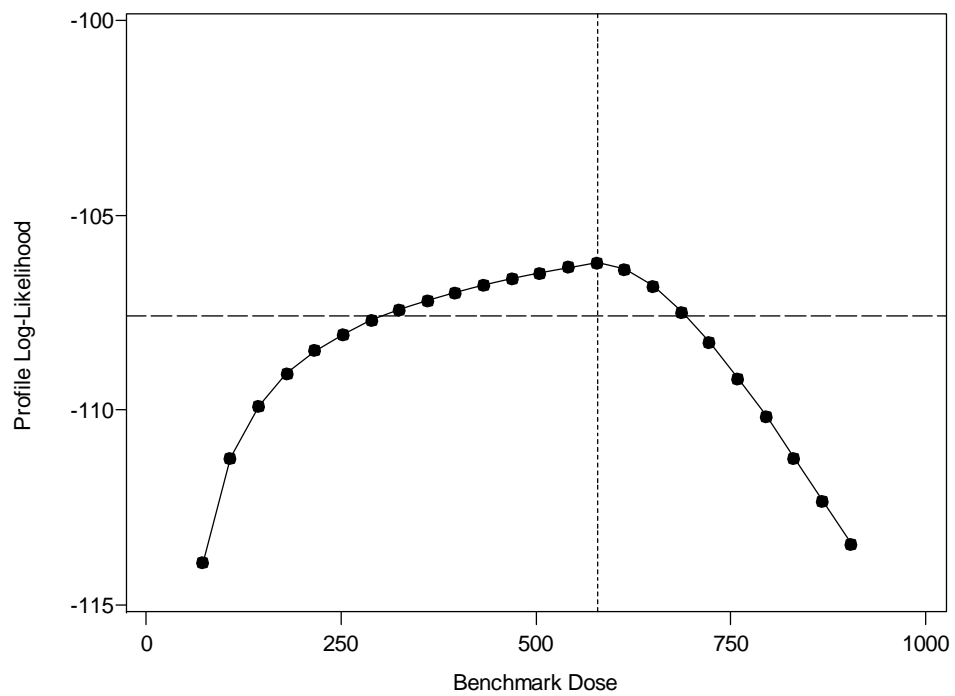
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



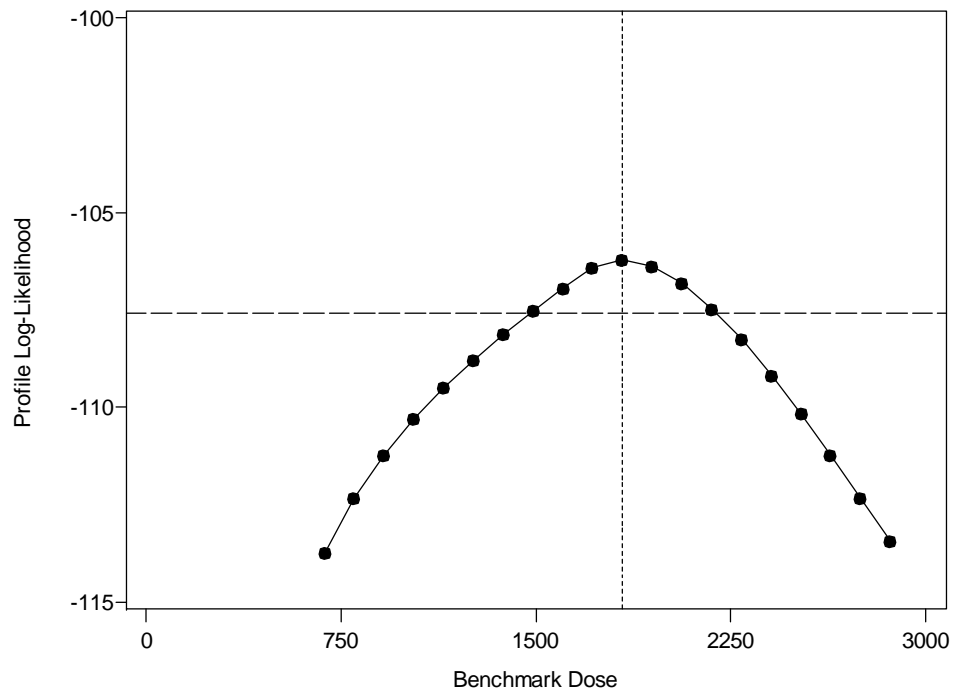
Incidental Extra Risk = 1.0E-04 at 104 Weeks



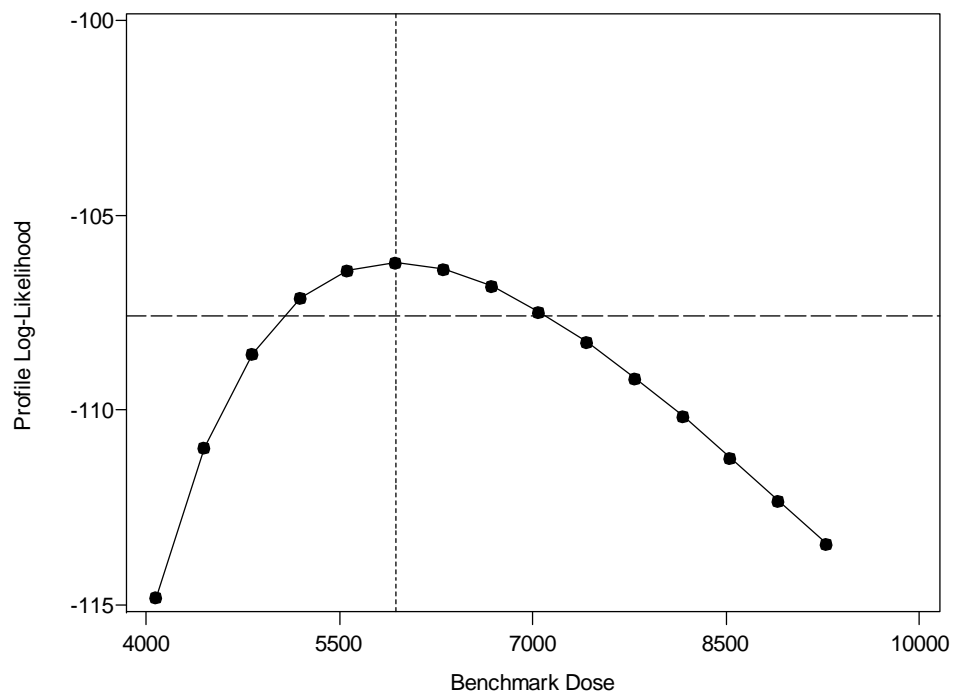
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A1.4. 1-Stage Model, Fixed $t_0 = 0$

A1.4.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-1.185389E+02	7.057911E+00	0	0.000000E+00
BMDS	-1.185389E+02	7.057911E+00	0	0.000000E+00

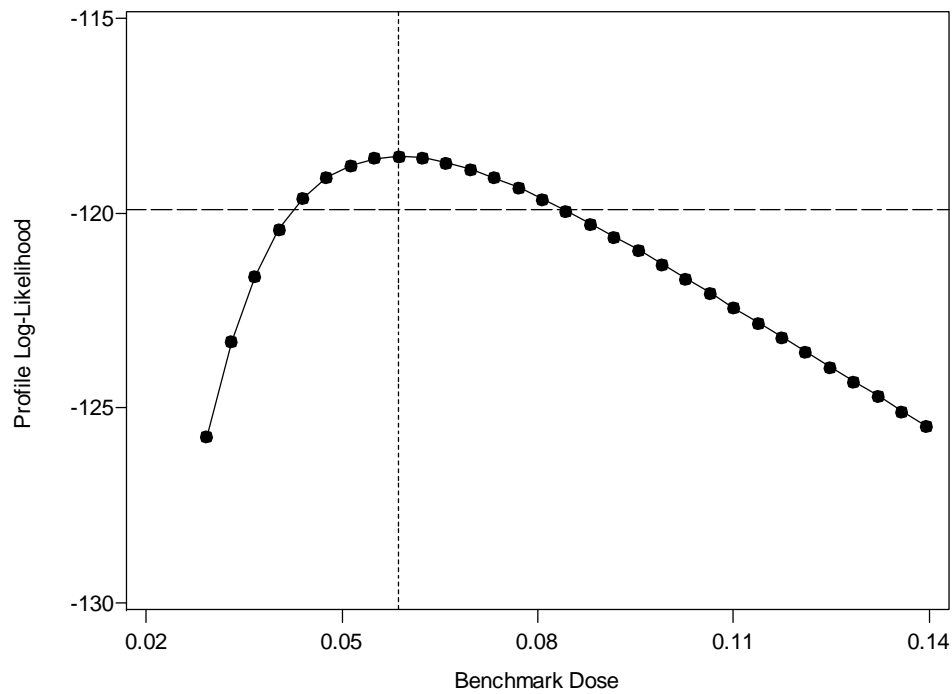
Software	Parameter MLE
	β_1
TOXRISK	9.881637E-17
BMDS	9.881635E-17

A1.4.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

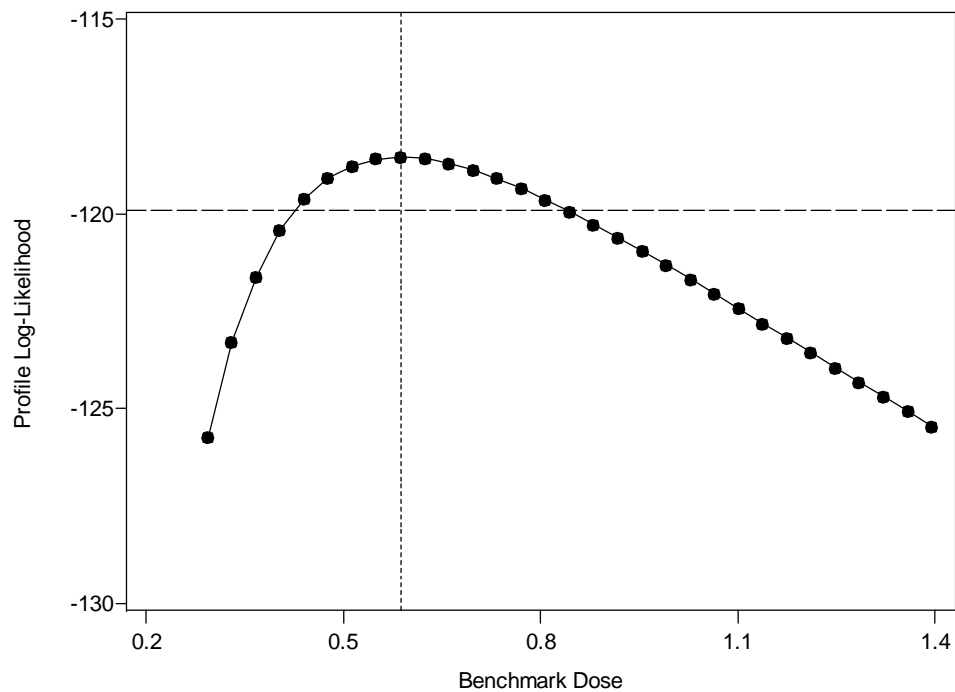
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	4.2649E-002	5.8766E-002	8.3923E-002
	BMDS	4.2649E-002	5.8766E-002	8.3913E-002
1.0E-05	TOXRISK	4.2649E-001	5.8767E-001	8.3915E-001
	BMDS	4.2649E-001	5.8767E-001	8.3914E-001
1.0E-04	TOXRISK	4.2651E+000	5.8769E+000	8.3917E+000
	BMDS	4.2651E+000	5.8769E+000	8.3917E+000
1.0E-03	TOXRISK	4.2670E+001	5.8796E+001	8.3955E+001
	BMDS	4.2671E+001	5.8796E+001	8.3955E+001
1.0E-02	TOXRISK	4.2863E+002	5.9062E+002	8.4336E+002
	BMDS	4.2864E+002	5.9062E+002	8.4336E+002
1.0E-01	TOXRISK	4.4935E+003	6.1917E+003	8.8411E+003
	BMDS	4.4936E+003	6.1917E+003	8.8411E+003

A1.4.3. Plots of Profile Log-Likelihood Functions

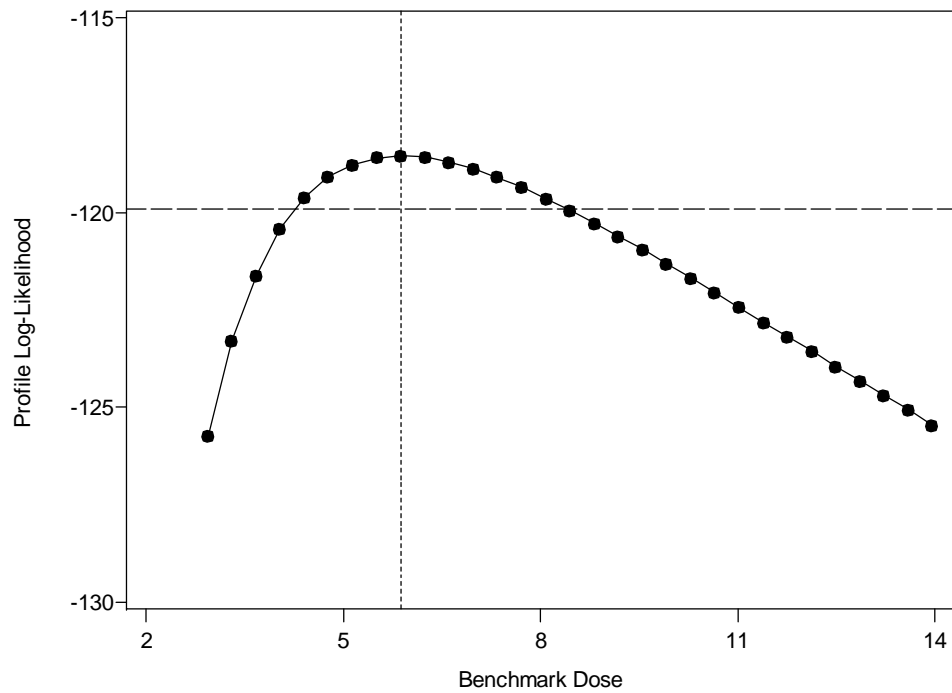
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



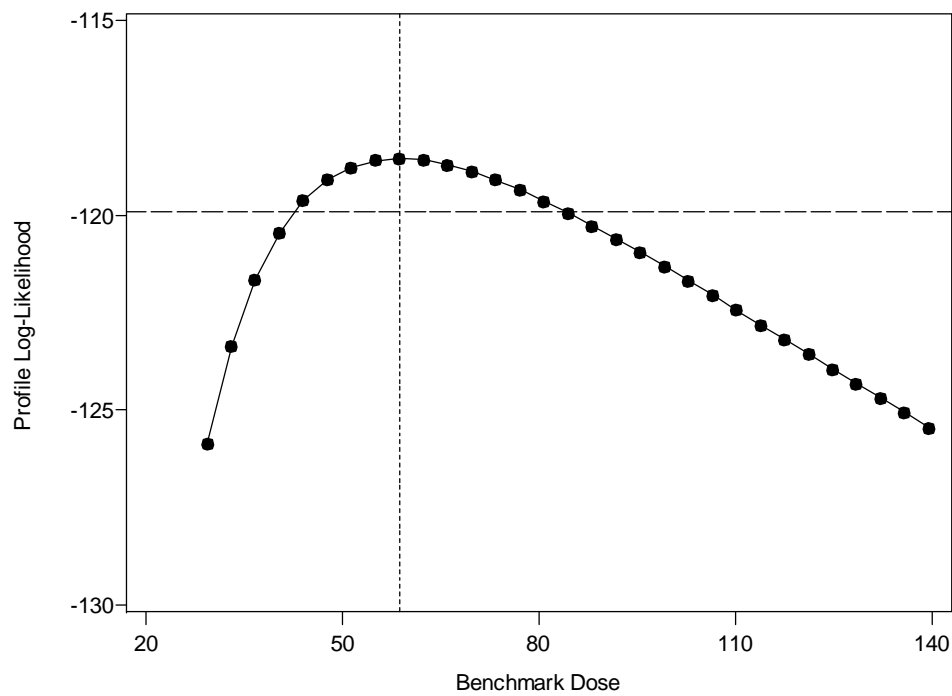
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



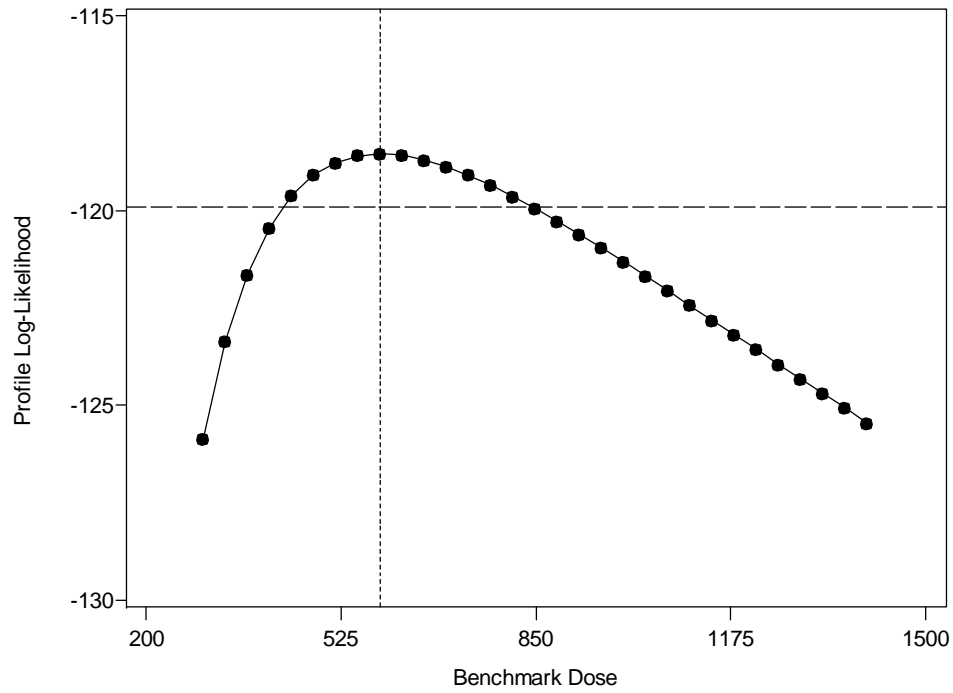
Incidental Extra Risk = 1.0E-04 at 104 Weeks



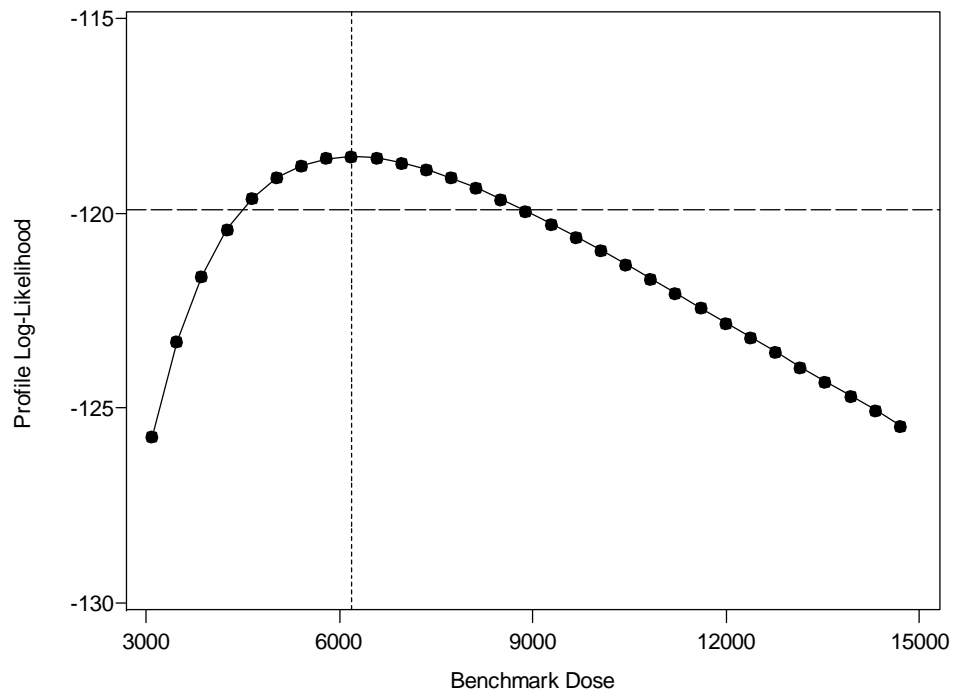
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A2. Female Mice Alveolar/Bronchiolar Aden/Carc (fm alvbr)

A2.1. 2-Stage Model, Fixed $t_0 = 0$

A2.1.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-5.951707E+001	2.314668E+000	0	1.853318E-006
BMDS	-5.951707E+001	2.314672E+000	0	1.853276E-006

Software	Parameter MLE	
	β_1	β_2
TOXRISK	0.000000E+000	1.448222E-007
BMDS	0.000000E+000	1.448193E-007

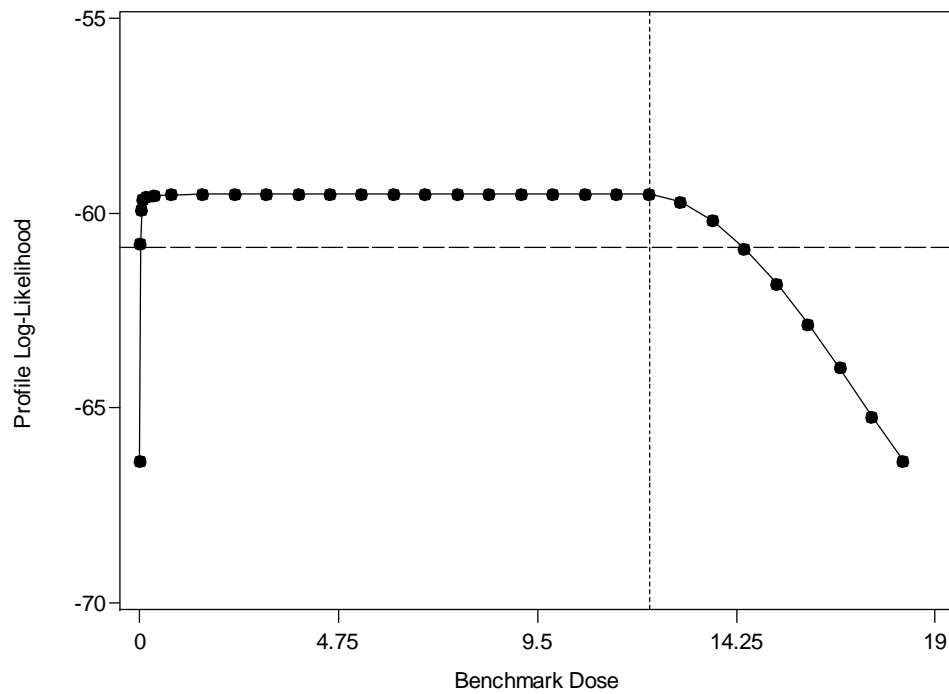
A2.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	2.2715E-002	1.2168E+001	1.5781E+001
	BMDS	2.2895E-002	1.2167E+001	1.4386E+001
1.0E-05	TOXRISK	2.2715E-001	3.8477E+001	4.9905E+001
	BMDS	2.2863E-001	3.8477E+001	4.5481E+001
1.0E-04	TOXRISK	2.2712E+000	1.2168E+002	1.5782E+002
	BMDS	2.2890E+000	1.2168E+002	1.4391E+002
1.0E-03	TOXRISK	2.2682E+001	3.8487E+002	4.9918E+002
	BMDS	2.2809E+001	3.8487E+002	4.5496E+002
1.0E-02	TOXRISK	2.2397E+002	1.2198E+003	1.5821E+003
	BMDS	2.2486E+002	1.2198E+003	1.4817E+003
1.0E-01	TOXRISK	2.0240E+003	3.9495E+003	5.1225E+003
	BMDS	2.0245E+003	3.9495E+003	4.6895E+003

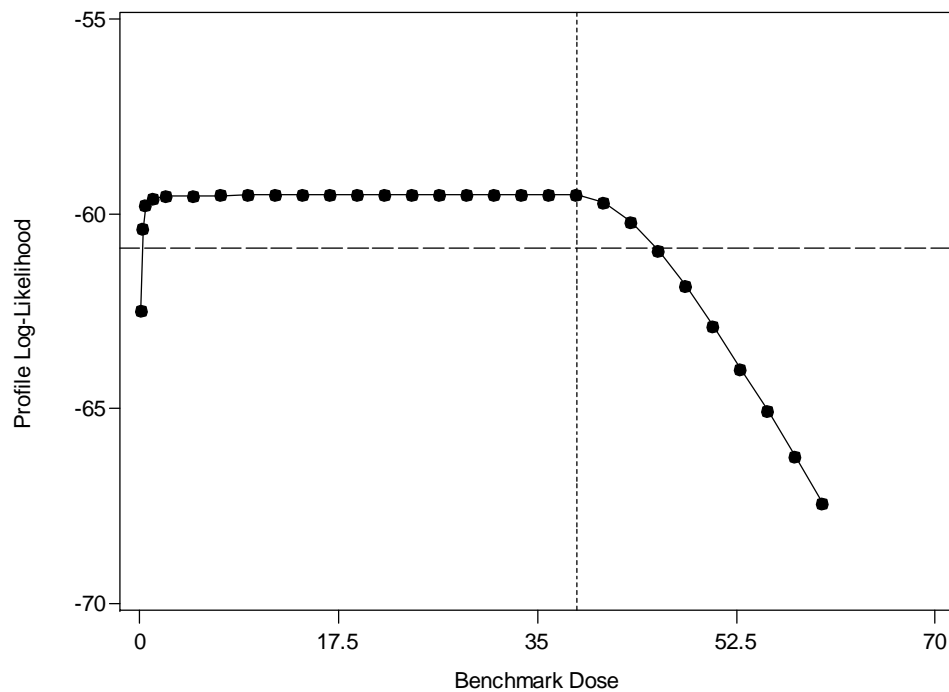
Incidental Extra Risk at 52 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	9.8154E-002	2.7139E+001	3.7279E+001
	BMDS	9.4485E-002	2.7139E+001	3.1000E+001
1.0E-05	TOXRISK	9.8143E-001	8.5821E+001	1.1789E+002
	BMDS	9.1044E-001	8.5821E+001	9.8507E+001
1.0E-04	TOXRISK	9.8032E+000	2.7140E+002	3.7280E+002
	BMDS	9.6131E+000	2.7140E+002	3.0823E+002
1.0E-03	TOXRISK	9.6947E+001	8.5842E+002	1.1792E+003
	BMDS	8.7145E+001	8.5843E+002	1.0026E+003
1.0E-02	TOXRISK	8.8153E+002	2.7207E+003	3.7373E+003
	BMDS	8.7855E+002	2.7207E+003	3.1386E+003
1.0E-01	TOXRISK	5.6804E+003	8.8091E+003	1.2101E+004
	BMDS	7.1639E+003	8.8091E+003	1.0336E+004

A2.1.3. Plots of Profile Log-Likelihood Functions

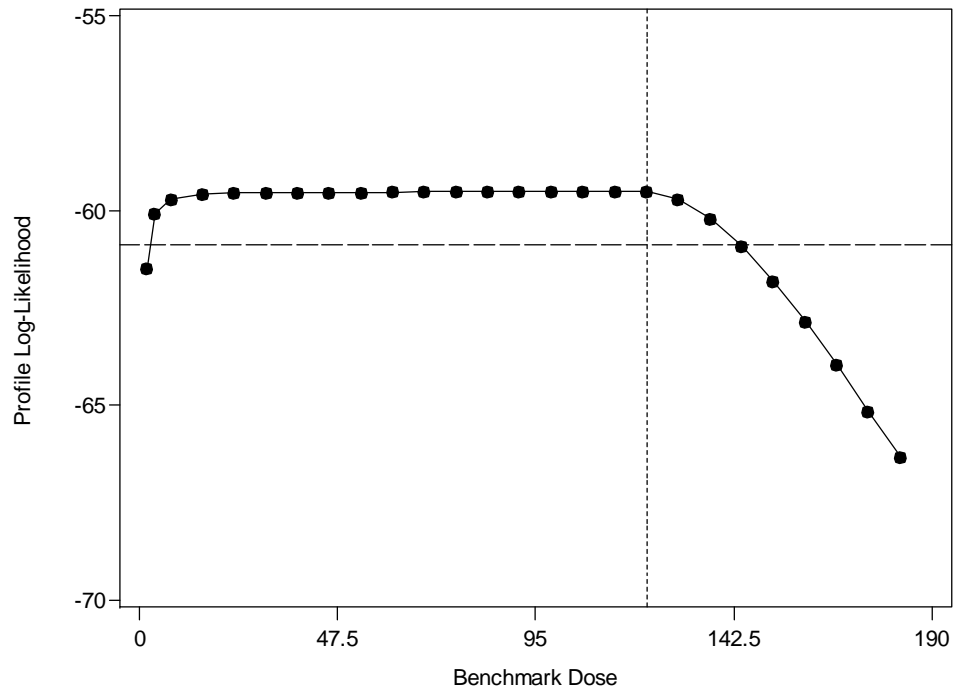
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



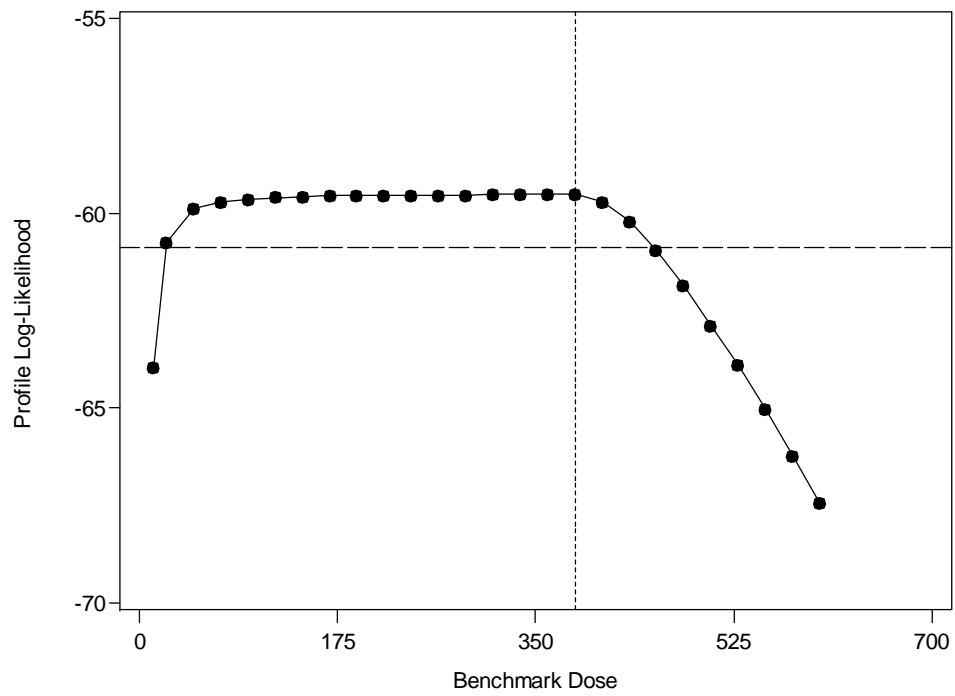
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



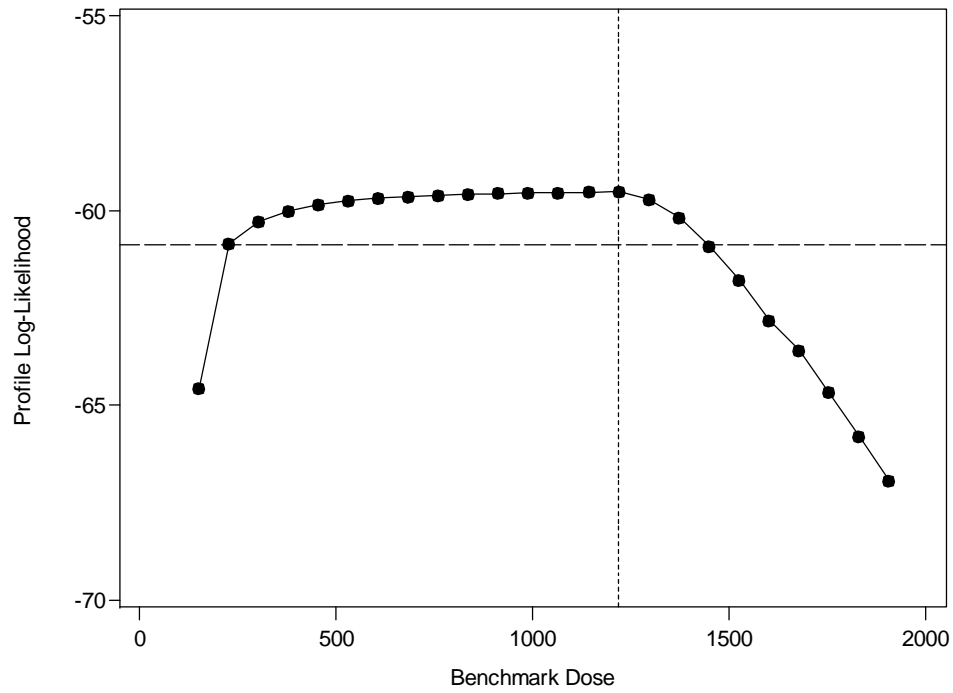
Incidental Extra Risk = 1.0E-04 at 104 Weeks



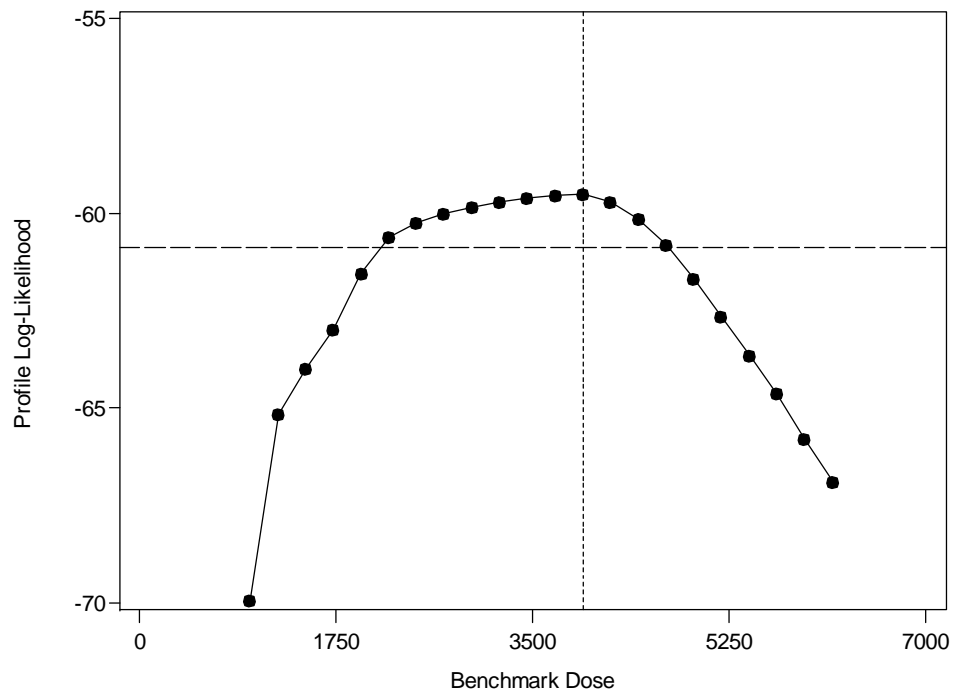
Incidental Extra Risk = 1.0E-03 at 104 Weeks



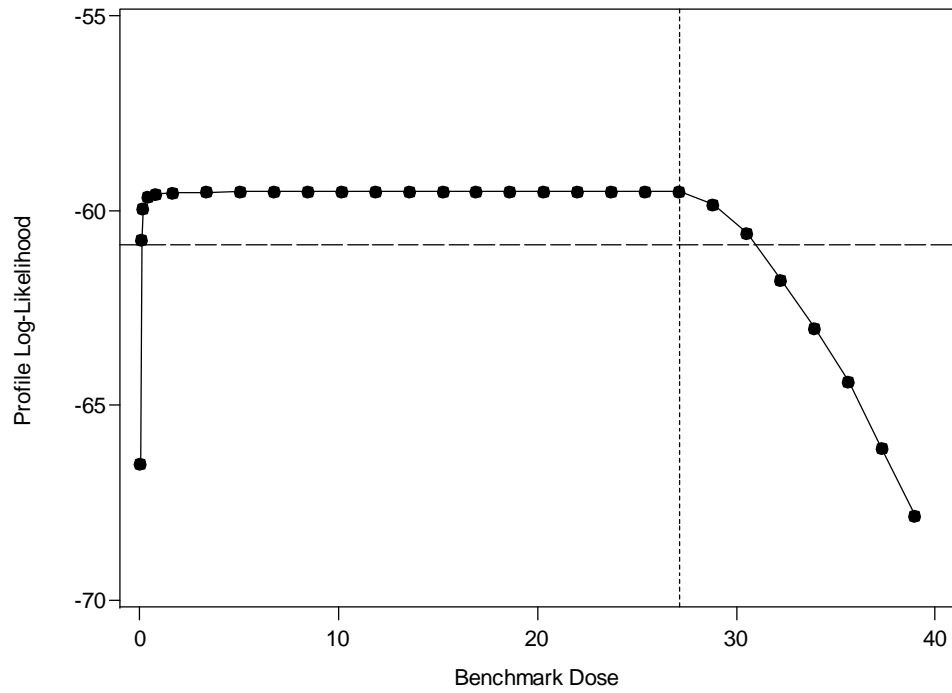
Incidental Extra Risk = 1.0E-02 at 104 Weeks



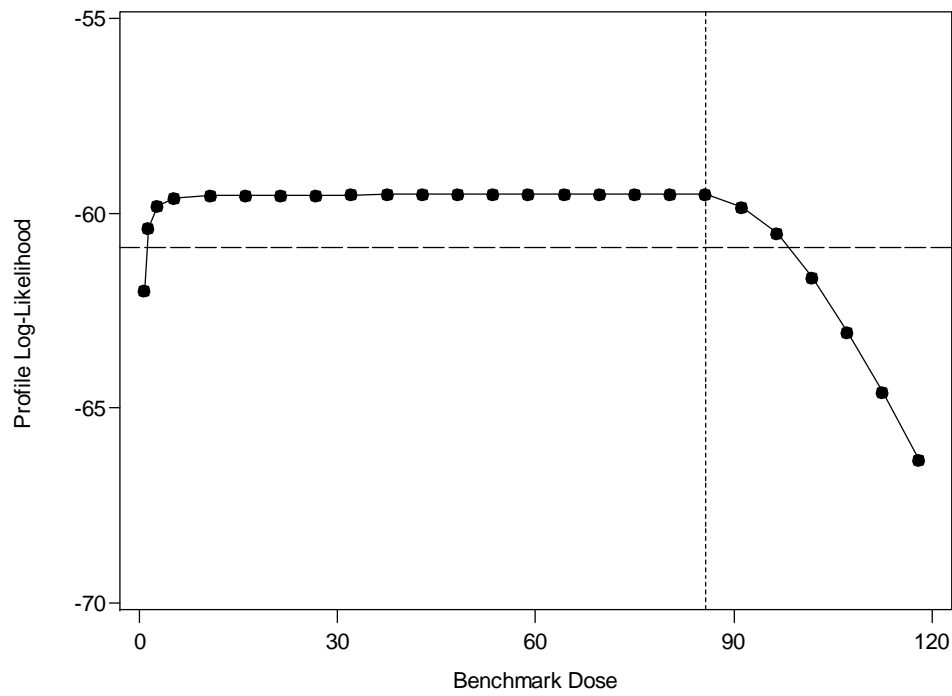
Incidental Extra Risk = 1.0E-01 at 104 Weeks



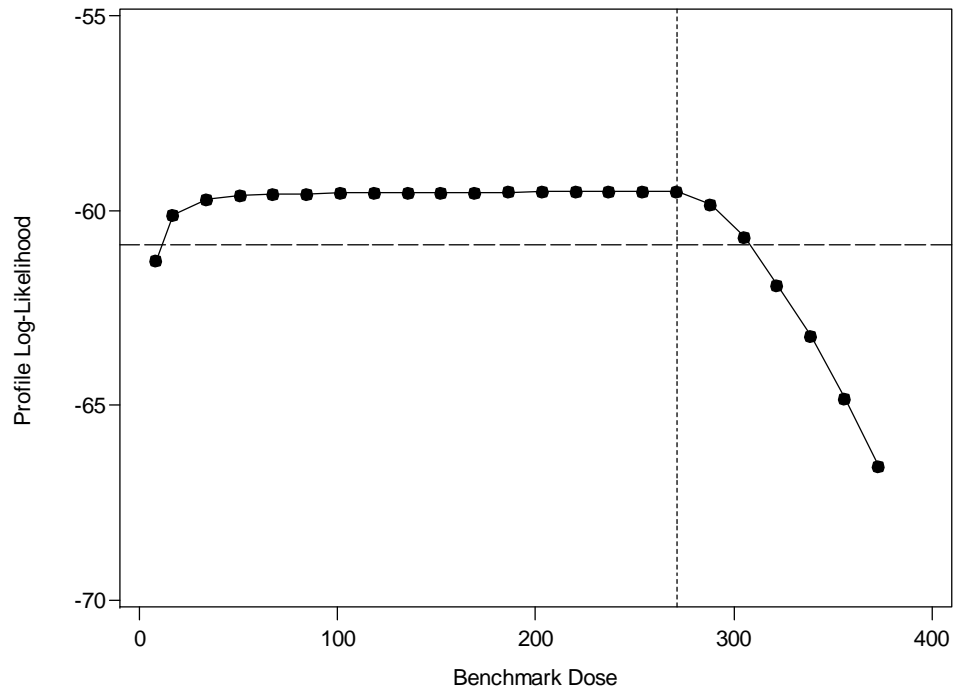
Incidental Extra Risk = $1.0\text{E-}06$ at 52 Weeks



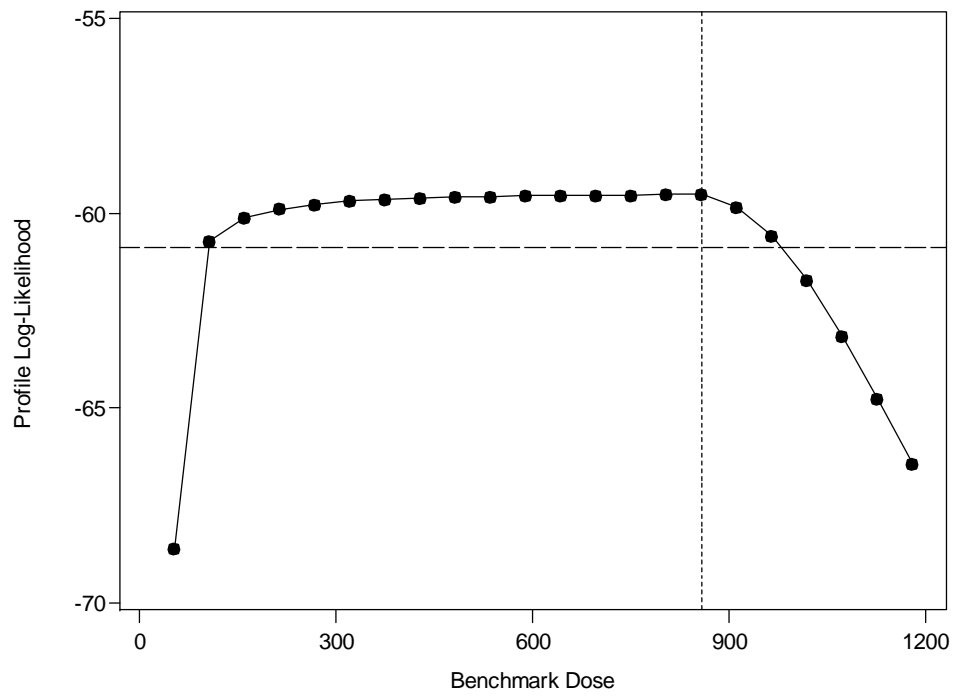
Incidental Extra Risk = $1.0\text{E-}05$ at 52 Weeks



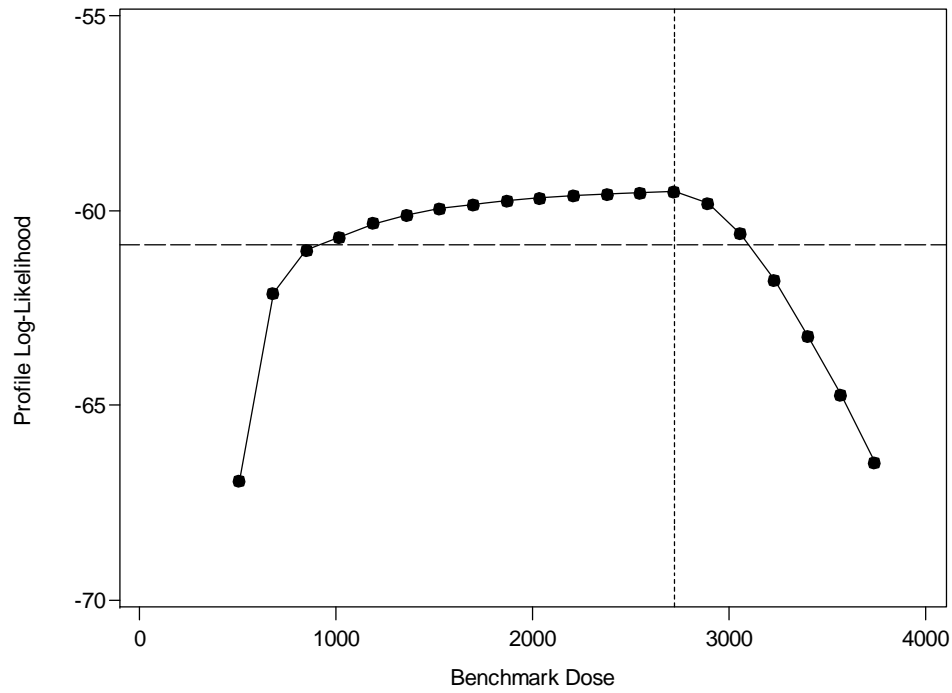
Incidental Extra Risk = 1.0E-04 at 52 Weeks



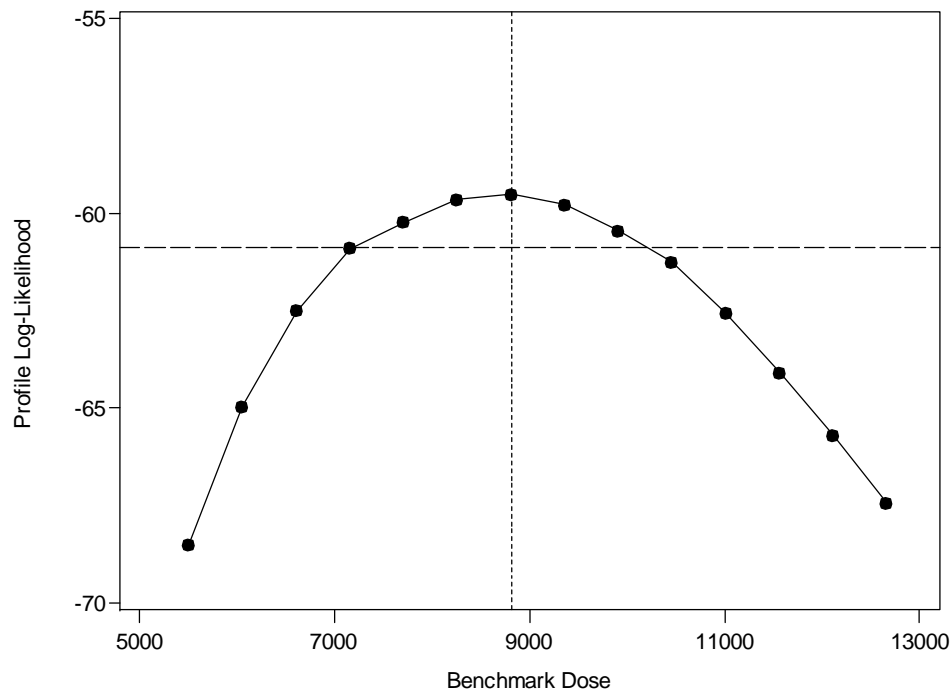
Incidental Extra Risk = 1.0E-03 at 52 Weeks



Incidental Extra Risk = $1.0E-02$ at 52 Weeks



Incidental Extra Risk = $1.0E-01$ at 52 Weeks



A2.2. 1-Stage Model, Fixed $t_0 = 0$

A2.2.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	B_0
TOXRISK	-6.447005E+001	1.000000E+000	0	6.493353E-004
BMDS	-6.447040E+001	1.000000E+000	0	6.480793E-004

Software	Parameter MLE
	β_1
TOXRISK	7.405624E-004
BMDS	7.436815E-004

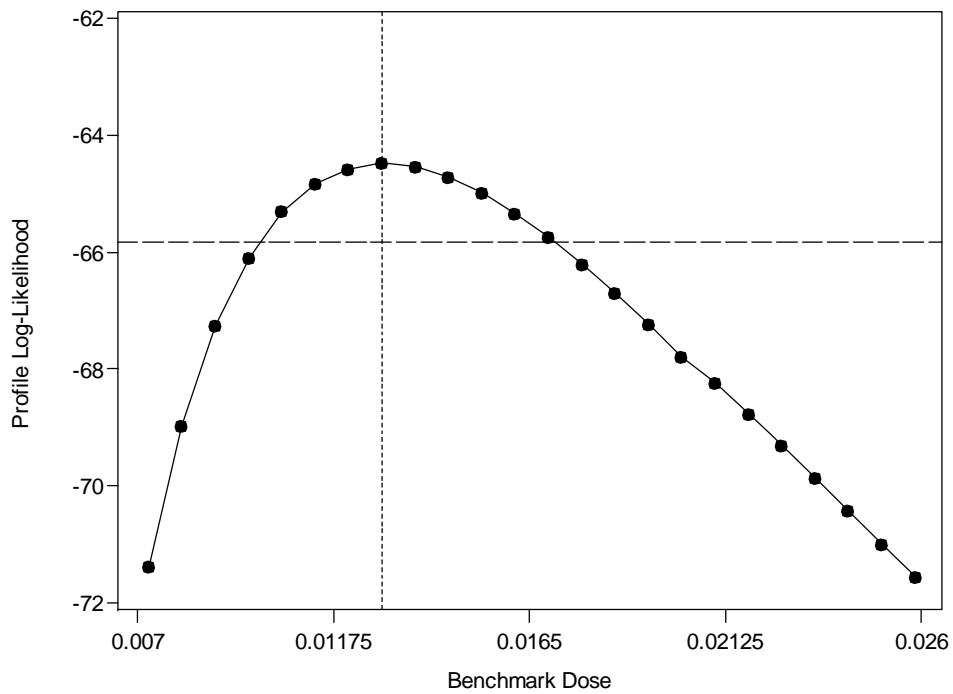
A2.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	9.2604E-003	1.2984E-002	1.7091E-002
	BMDS	9.9383E-003	1.2929E-002	1.7133E-002
1.0E-05	TOXRISK	9.2604E-002	1.2984E-001	1.7136E-001
	BMDS	9.9349E-002	1.2930E-001	1.7128E-001
1.0E-04	TOXRISK	9.2609E-001	1.2985E+000	1.7131E+000
	BMDS	9.9340E-001	1.2930E+000	1.7130E+000
1.0E-03	TOXRISK	9.2650E+000	1.2990E+001	1.7138E+001
	BMDS	9.9397E+000	1.2936E+001	1.7138E+001
1.0E-02	TOXRISK	9.3070E+001	1.3049E+002	1.7216E+002
	BMDS	9.9848E+001	1.2995E+002	1.7183E+002
1.0E-01	TOXRISK	9.7568E+002	1.3680E+003	1.8048E+003
	BMDS	1.0467E+003	1.3623E+003	1.7995E+003

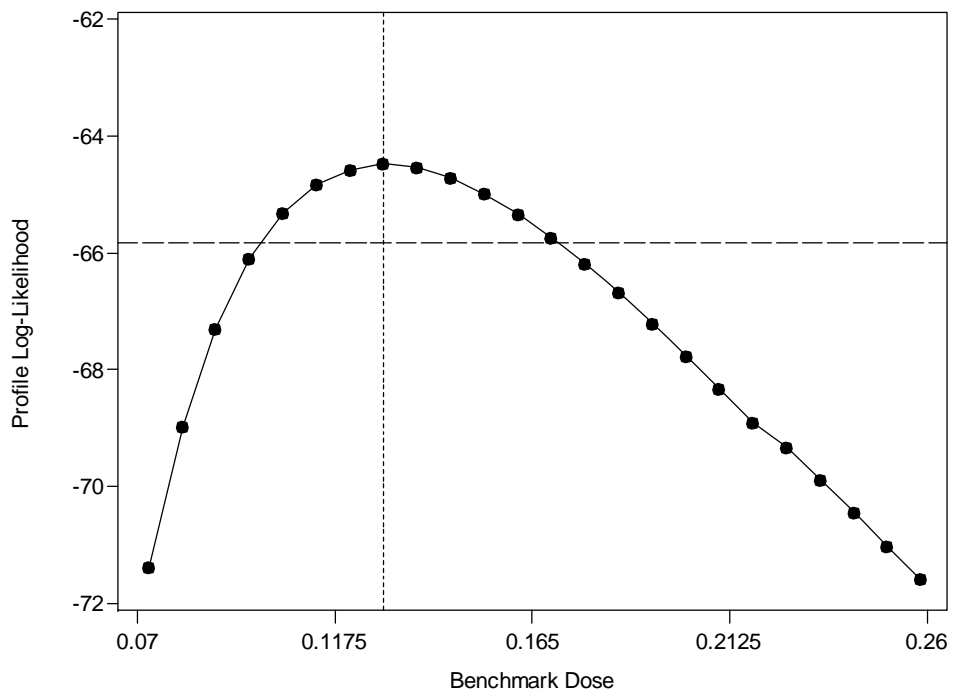
Incidental Extra Risk at 52 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	2.1290E-002	2.5968E-002	4.0574E-002
	BMDS	2.0329E-002	2.5859E-002	3.4779E-002
1.0E-05	TOXRISK	2.1290E-001	2.5968E-001	4.0608E-001
	BMDS	2.0494E-001	2.5859E-001	3.4691E-001
1.0E-04	TOXRISK	2.1291E+000	2.5969E+000	4.0609E+000
	BMDS	2.0508E+000	2.5860E+000	3.4881E+000
1.0E-03	TOXRISK	2.1301E+001	2.5981E+001	4.0627E+001
	BMDS	2.0382E+001	2.5872E+001	3.4800E+001
1.0E-02	TOXRISK	2.1397E+002	2.6099E+002	4.0811E+002
	BMDS	2.0464E+002	2.5989E+002	3.4865E+002
1.0E-01	TOXRISK	2.2432E+003	2.7360E+003	4.2783E+003
	BMDS	2.1401E+003	2.7245E+003	3.6749E+003

A2.2.3. Plots of Profile Log-Likelihood Functions

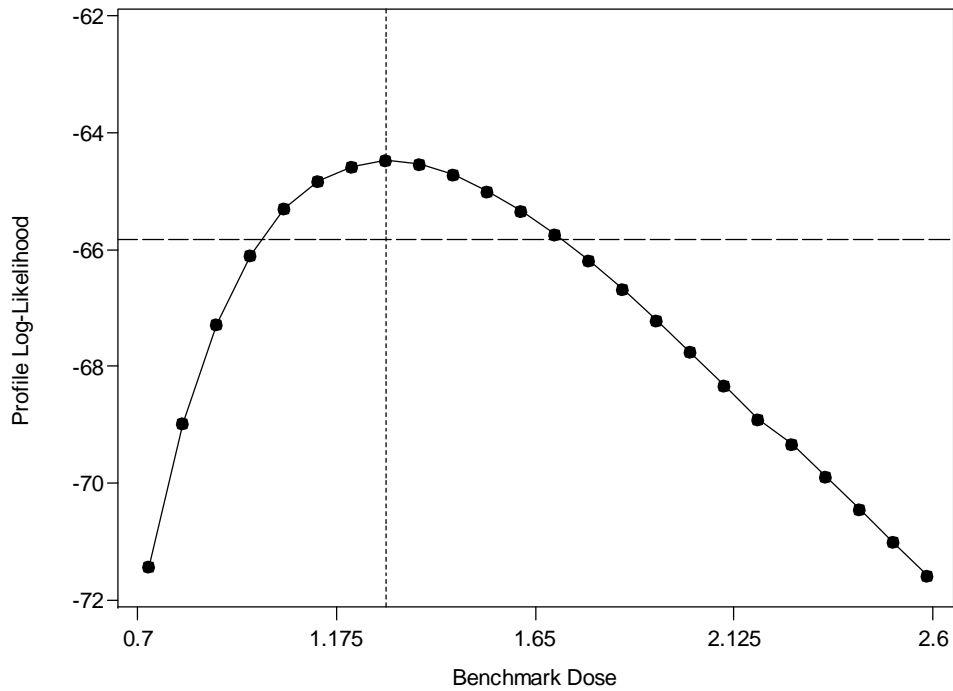
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



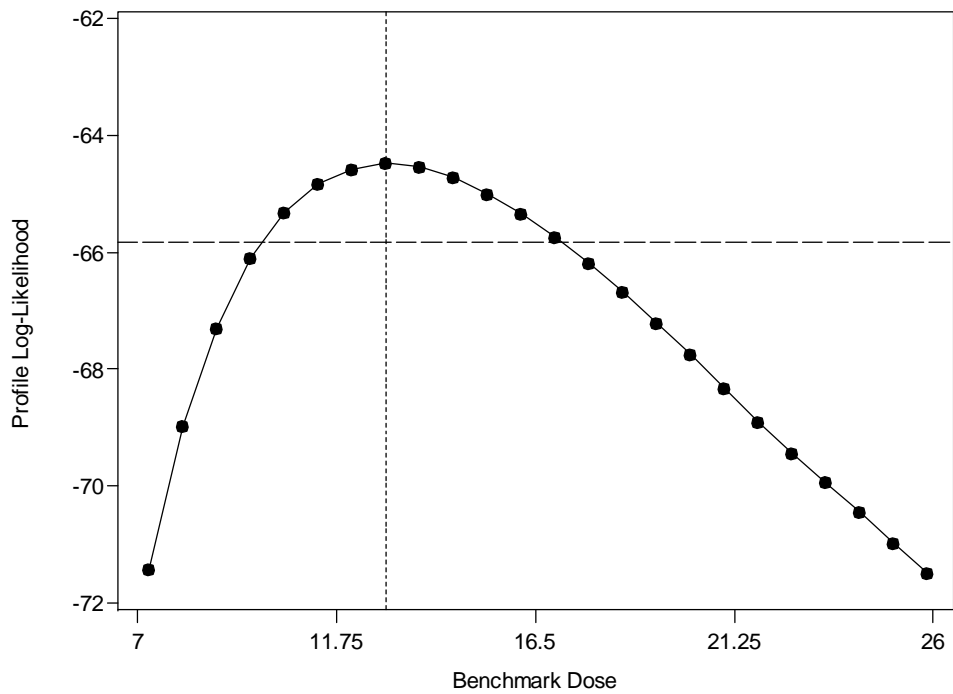
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



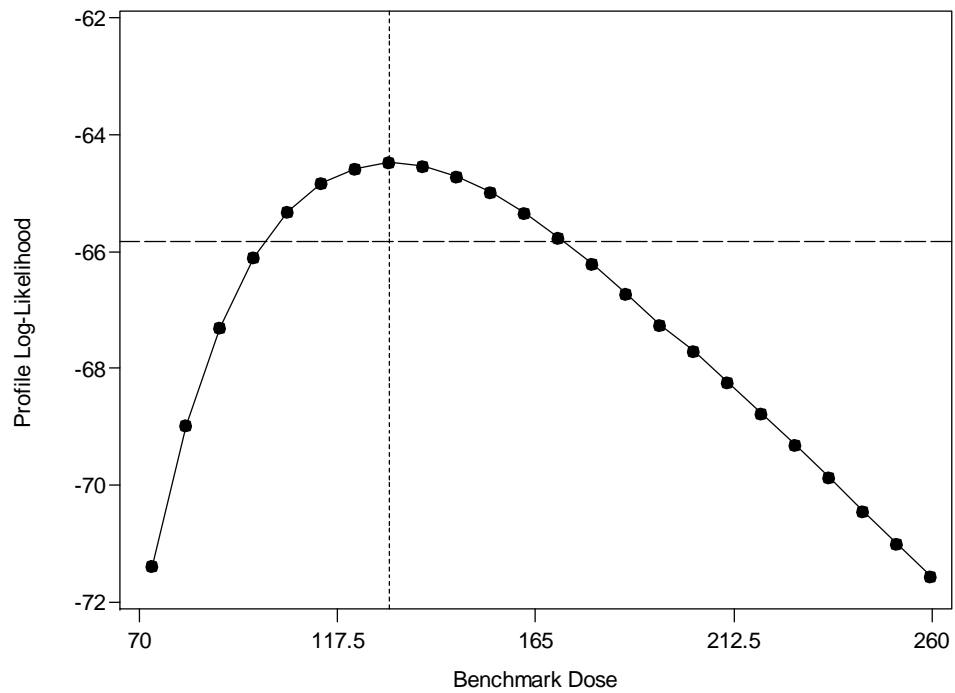
Incidental Extra Risk = 1.0E-04 at 104 Weeks



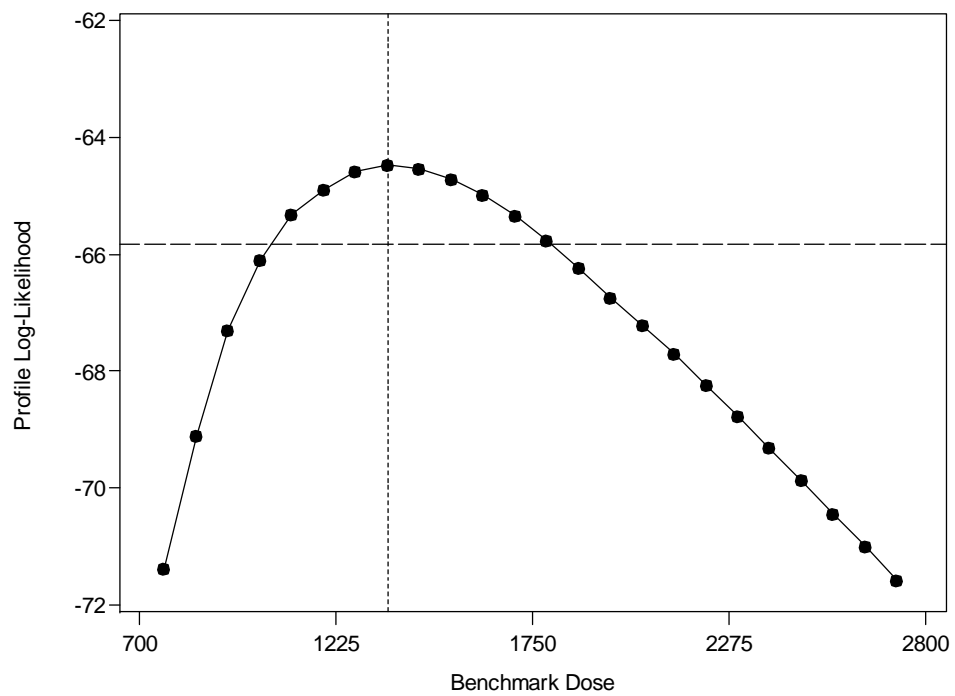
Incidental Extra Risk = 1.0E-03 at 104 Weeks



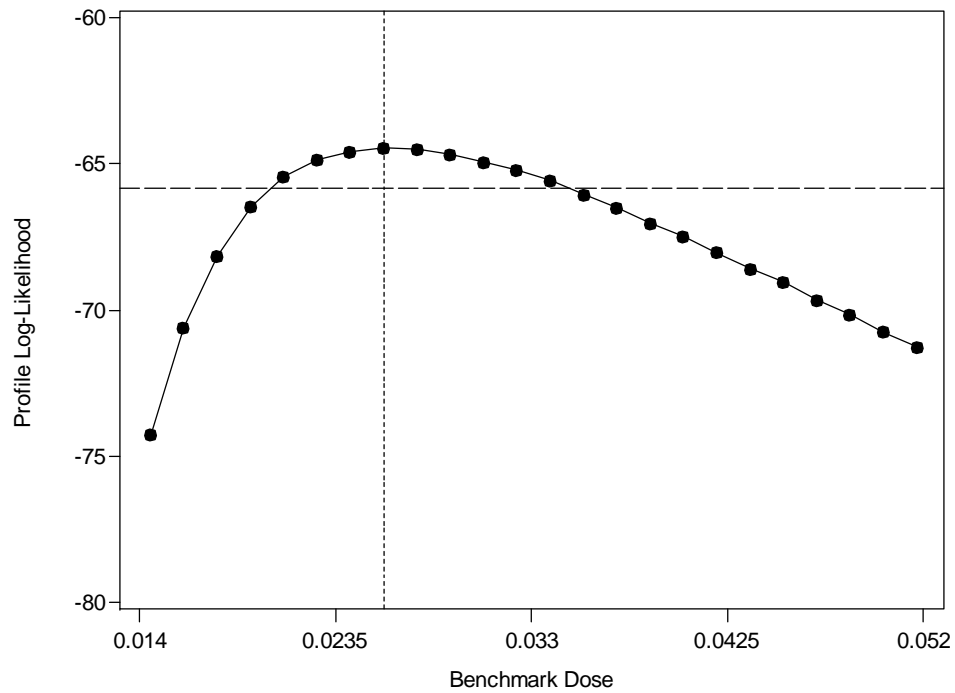
Incidental Extra Risk = 1.0E-02 at 104 Weeks



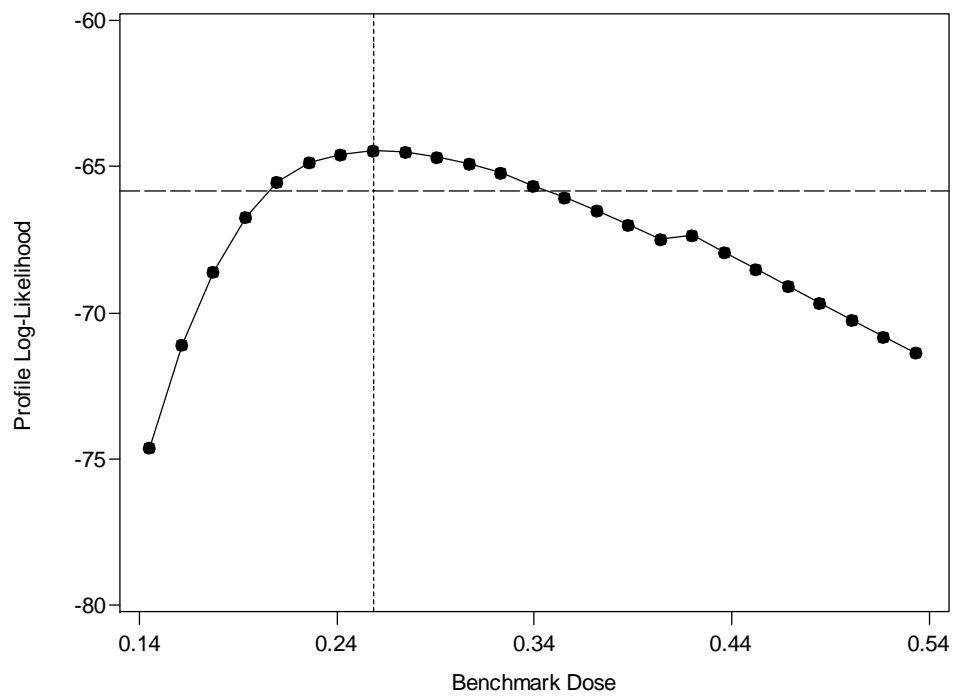
Incidental Extra Risk = 1.0E-01 at 104 Weeks



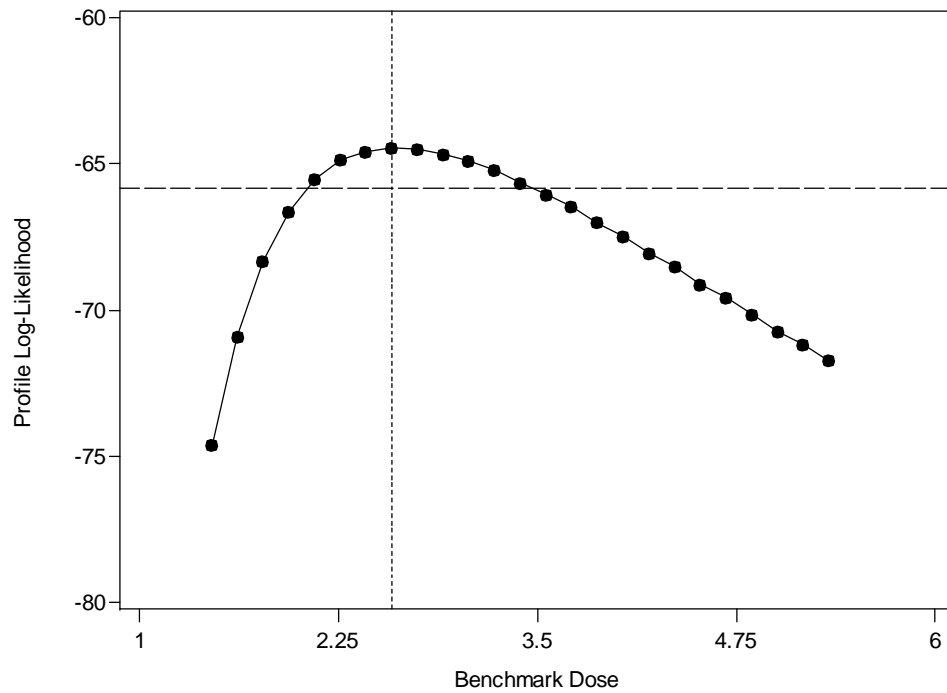
Incidental Extra Risk = 1.0E-06 at 52 Weeks



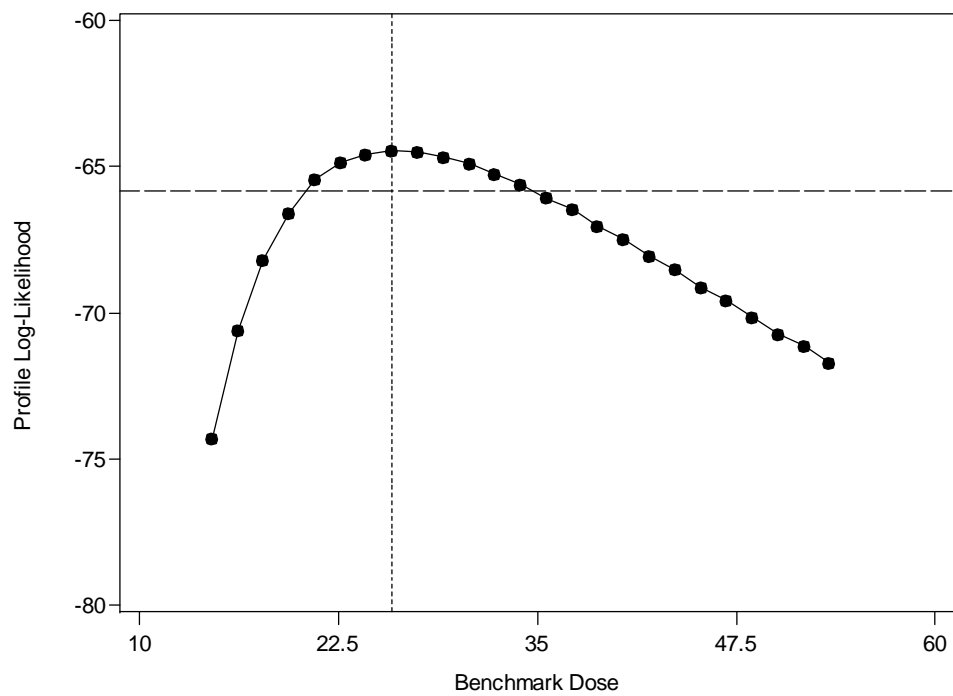
Incidental Extra Risk = 1.0E-05 at 52 Weeks



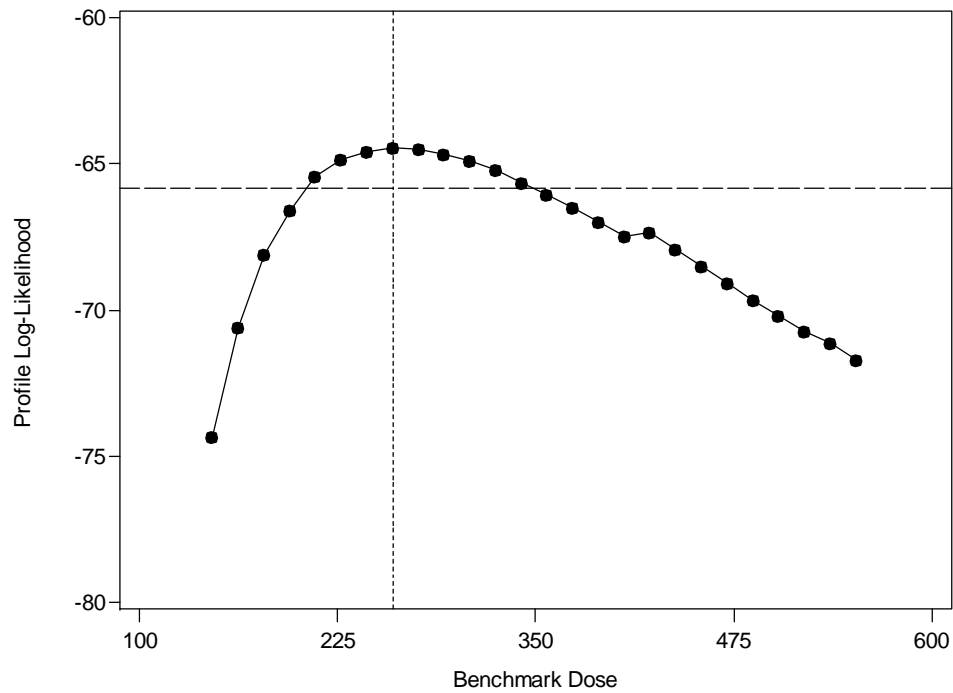
Incidental Extra Risk = 1.0E-04 at 52 Weeks



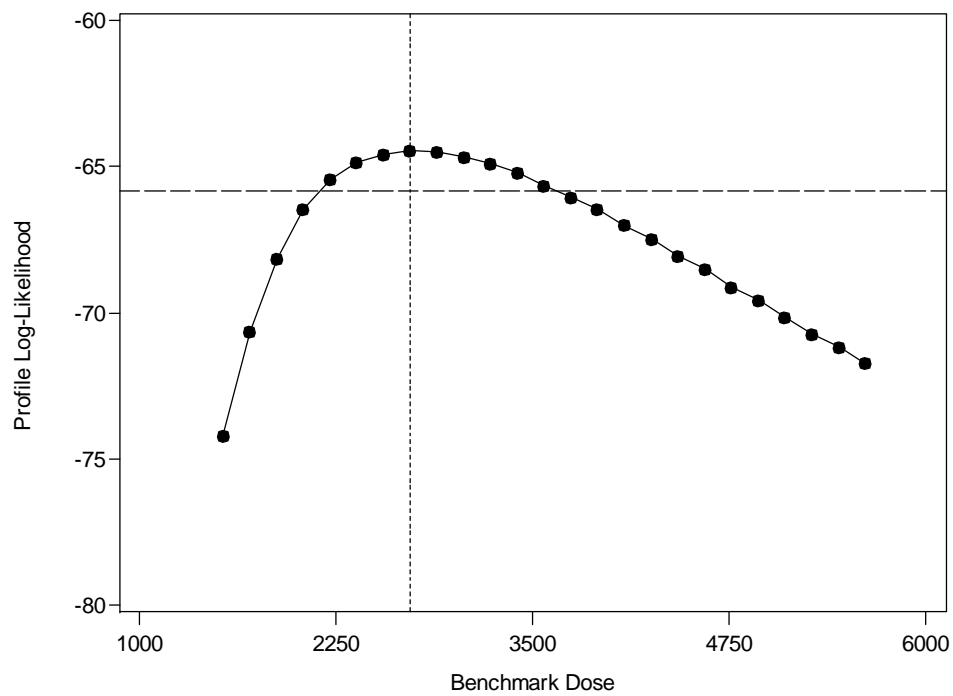
Incidental Extra Risk = 1.0E-03 at 52 Weeks



Incidental Extra Risk = 1.0E-02 at 52 Weeks



Incidental Extra Risk = 1.0E-01 at 52 Weeks



A3. Female Mice Hemangiosarcomas (fm hemang)

A3.1. 2-Stage Model, Fixed $t_0 = 0$

A3.1.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	T_0	β_0
TOXRISK	-5.860802E+001	3.031619E+000	0	0.000000E+000
BMDs	-5.860802E+001	3.031616E+000	0	0.000000E+000

Software	Parameter MLE	
	β_1	β_2
TOXRISK	1.403519E-007	4.964347E-009
BMDs	1.403537E-007	4.964385E-009

A3.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

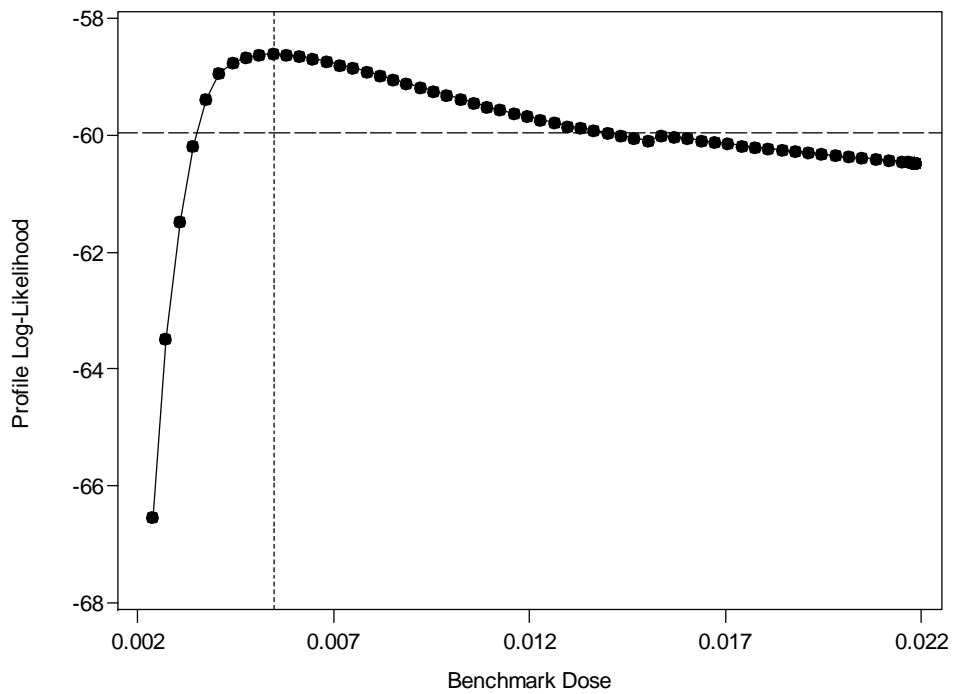
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	3.2723E-003	5.4690E-003	1.5161E-002
	BMDs	3.4877E-003	5.4690E-003	1.5146E-002
1.0E-05	TOXRISK	3.2723E-002	5.4690E-002	1.5148E-001
	BMDs	3.4943E-002	5.4690E-002	1.5142E-001
1.0E-04	TOXRISK	3.2724E-001	5.4691E-001	1.5134E+000
	BMDs	3.4182E-001	5.4691E-001	1.5134E+000
1.0E-03	TOXRISK	3.2739E+000	5.4707E+000	1.5027E+001
	BMDs	3.2759E+000	5.4706E+000	1.5019E+001
1.0E-02	TOXRISK	3.2887E+001	5.4859E+001	1.4121E+002
	BMDs	3.2897E+001	5.4859E+001	1.4120E+002
1.0E-01	TOXRISK	3.4477E+002	5.6493E+002	1.0608E+003
	BMDs	3.3398E+002	5.6493E+002	1.0607E+003

Incidental Extra Risk	Software	BMD		
		Lower 95%	MLE	Upper 95%

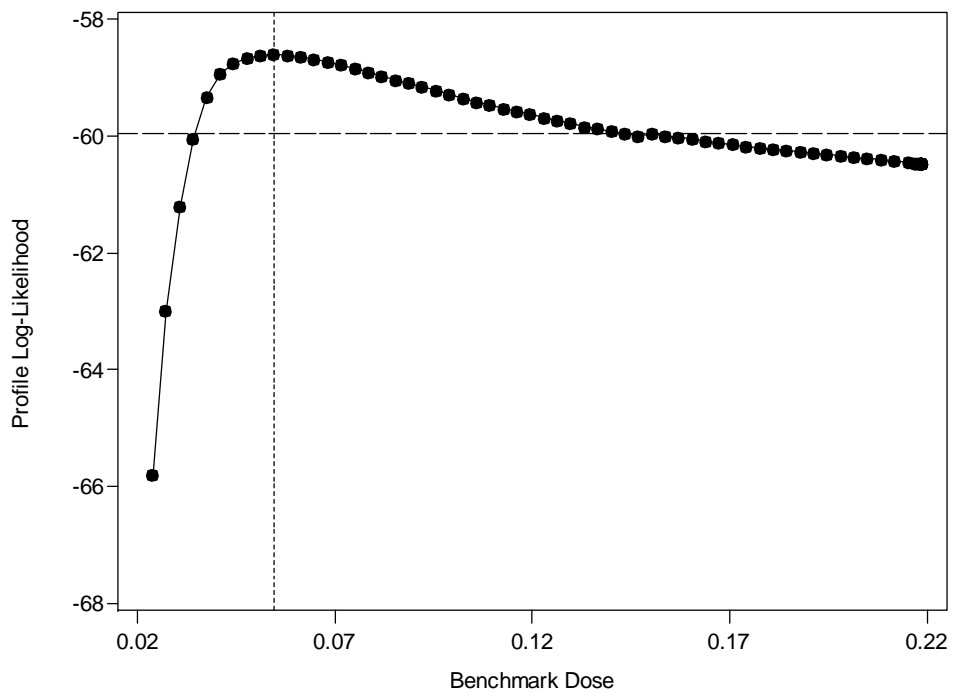
at 52 Weeks		Bound		Bound
1.0E-06	TOXRISK	1.6365E-002	4.4721E-002	2.4640E-001
	BMDS	2.4467E-002	4.4721E-002	4.5813E-001
1.0E-05	TOXRISK	1.6365E-001	4.4721E-001	2.4627E+000
	BMDS	2.2764E-001	4.4721E-001	4.5718E+000
1.0E-04	TOXRISK	1.6366E+000	4.4716E+000	2.4472E+001
	BMDS	2.2424E+000	4.4716E+000	4.4815E+001
1.0E-03	TOXRISK	1.6373E+001	4.4673E+001	2.3120E+002
	BMDS	2.4528E+001	4.4673E+001	3.8592E+002
1.0E-02	TOXRISK	1.6447E+002	4.4254E+002	1.7005E+003
	BMDS	2.2737E+002	4.4254E+002	2.3140E+003
1.0E-01	TOXRISK	1.7242E+003	4.1134E+003	8.8863E+003
	BMDS	2.3424E+003	4.1134E+003	1.0681E+004

A3.1.3. Plots of Profile Log-Likelihood Functions

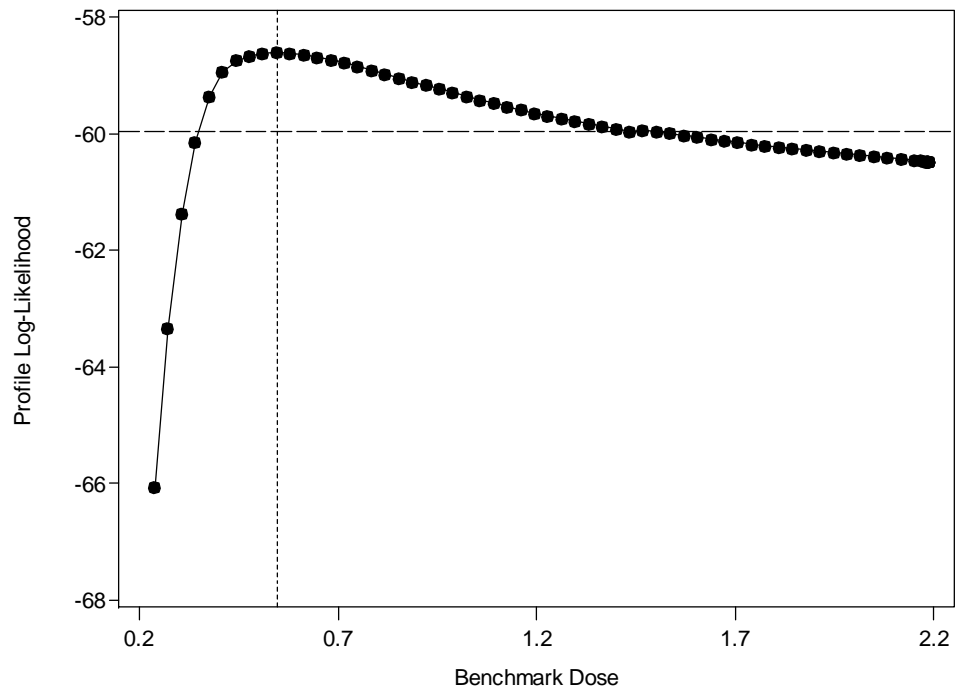
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



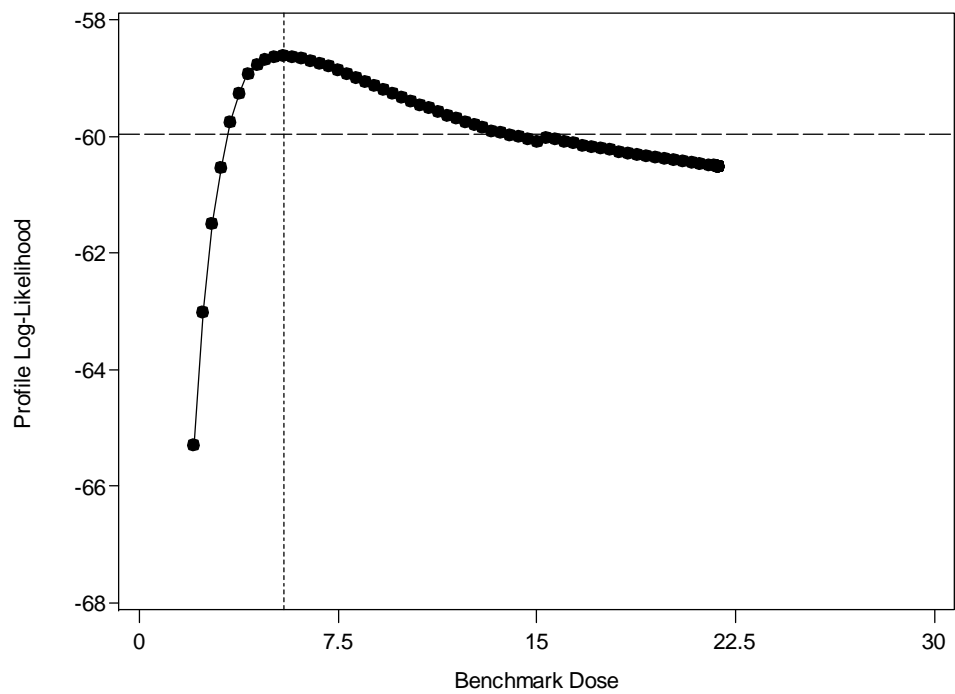
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



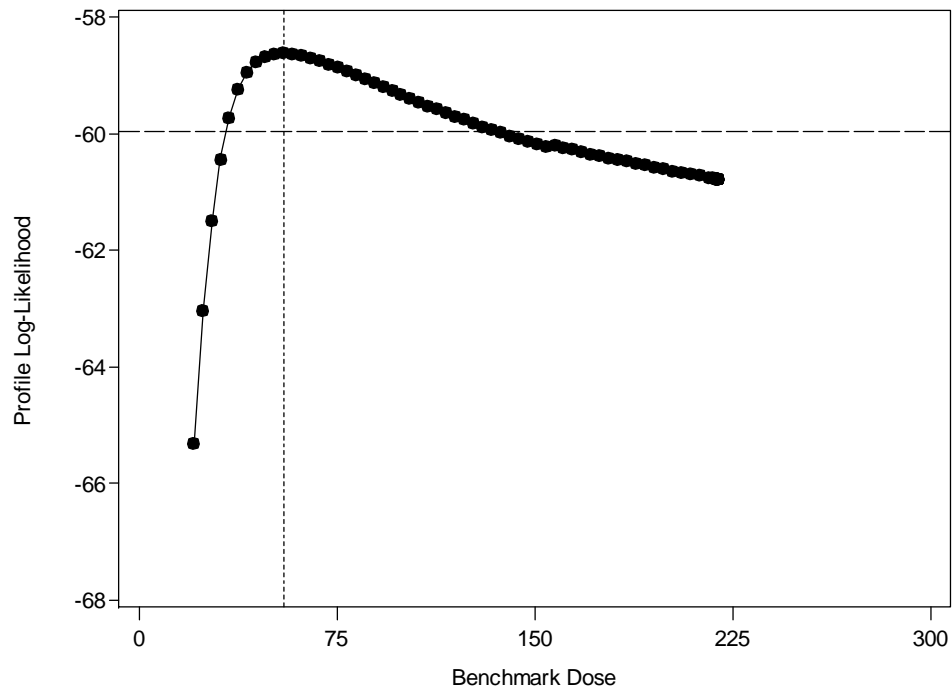
Incidental Extra Risk = $1.0\text{E-}04$ at 104 Weeks



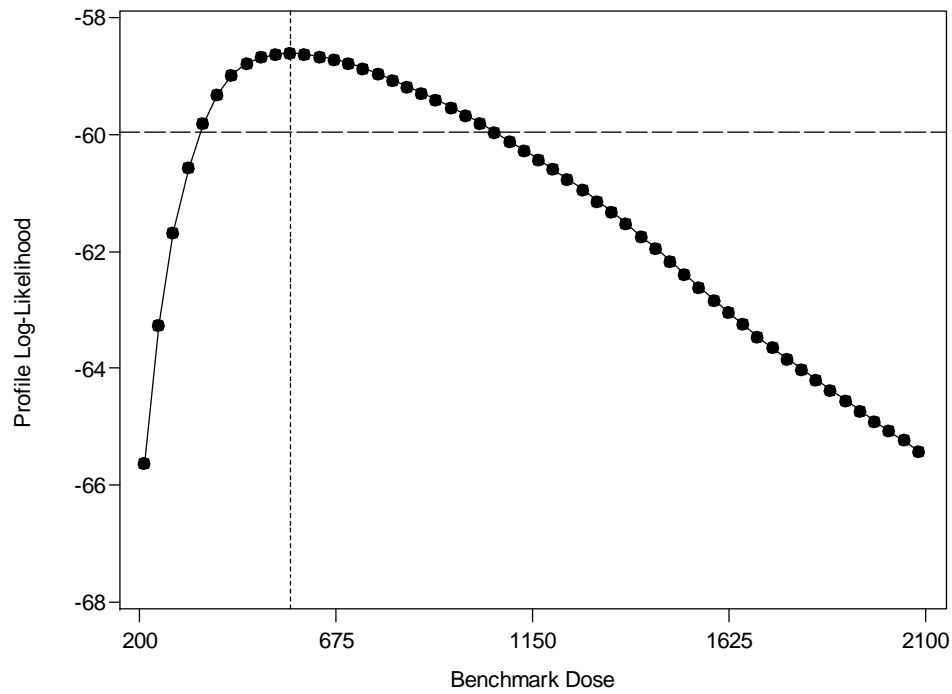
Incidental Extra Risk = $1.0\text{E-}03$ at 104 Weeks



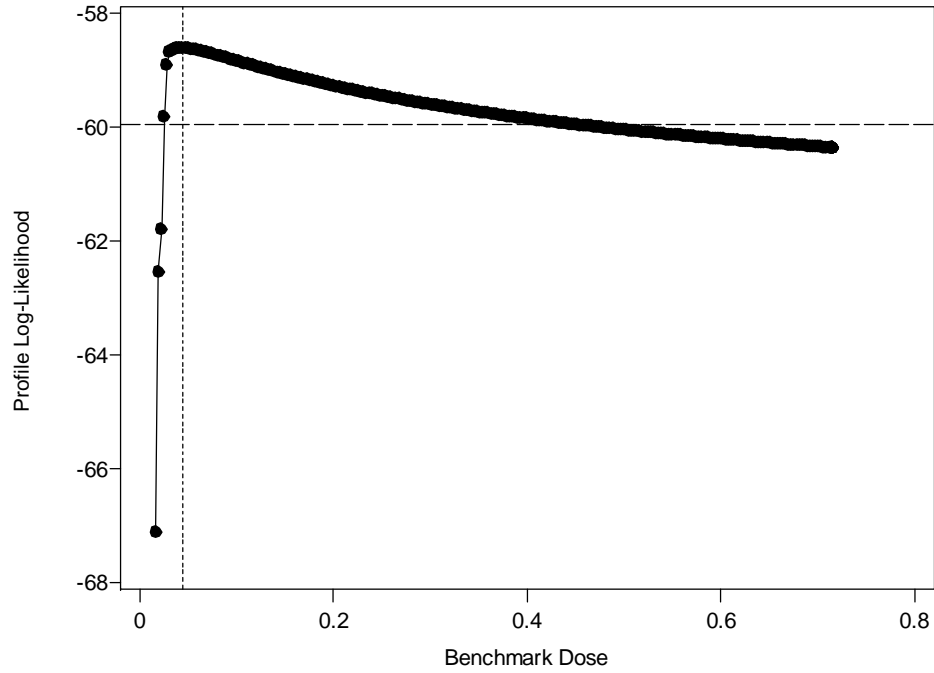
Incidental Extra Risk = 1.0E-02 at 104 Weeks



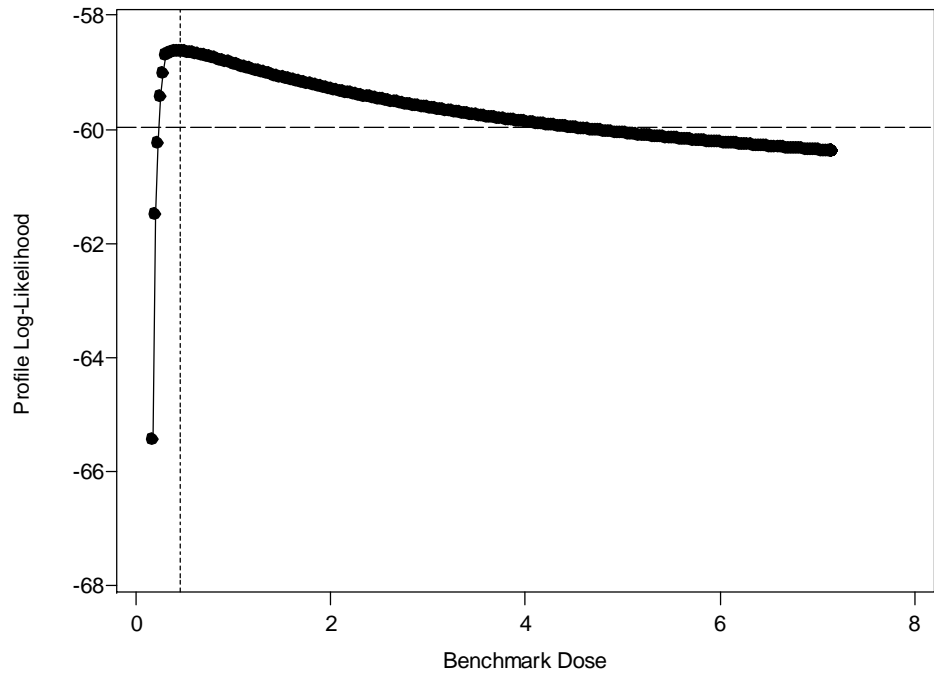
Incidental Extra Risk = 1.0E-01 at 104 Weeks



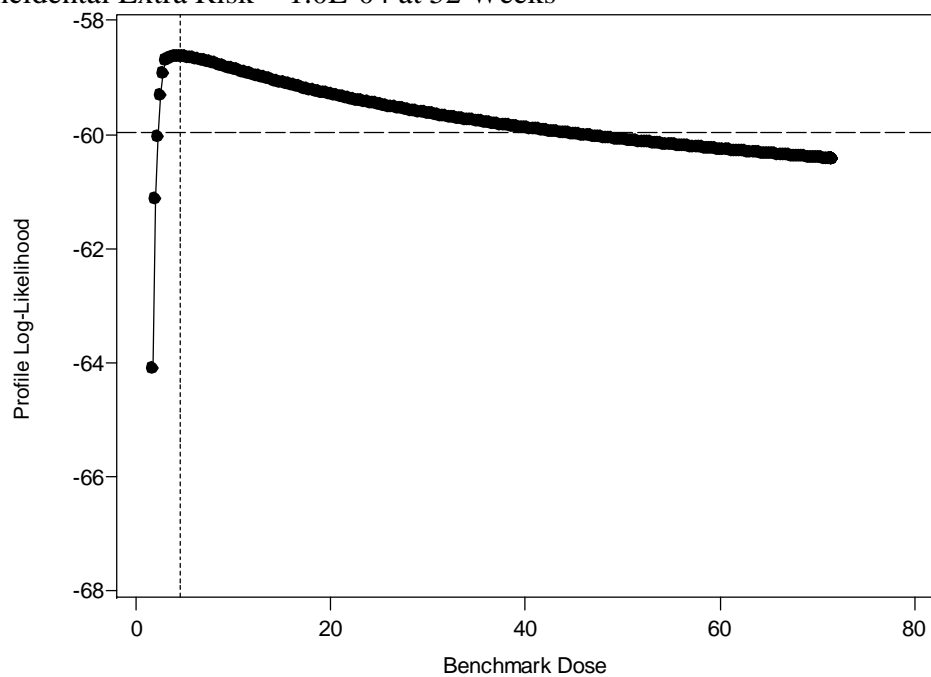
Incidental Extra Risk = 1.0E-06 at 52 Weeks



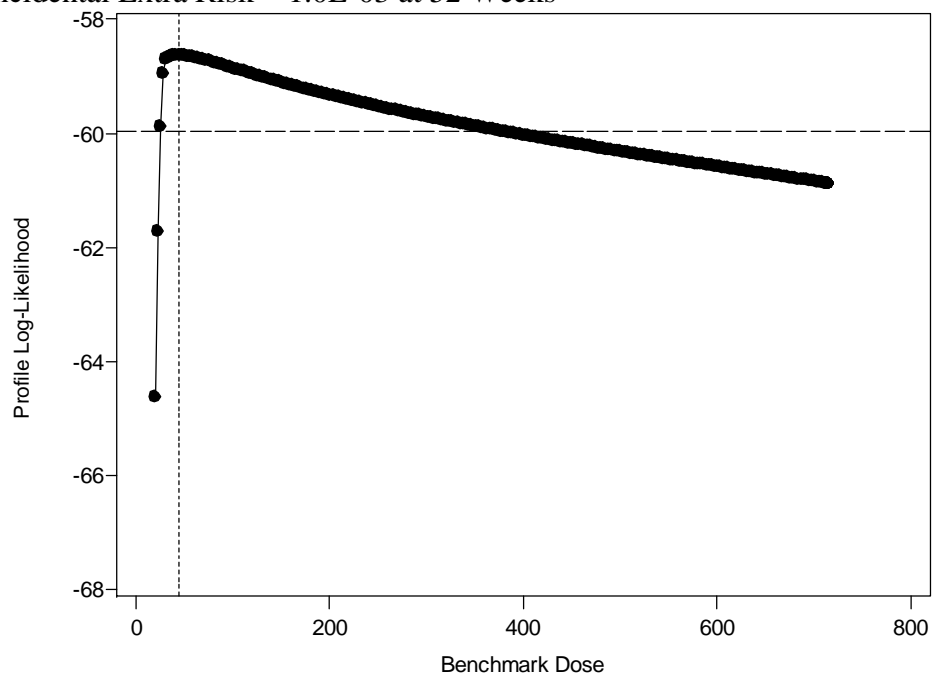
Incidental Extra Risk = 1.0E-05 at 52 Weeks



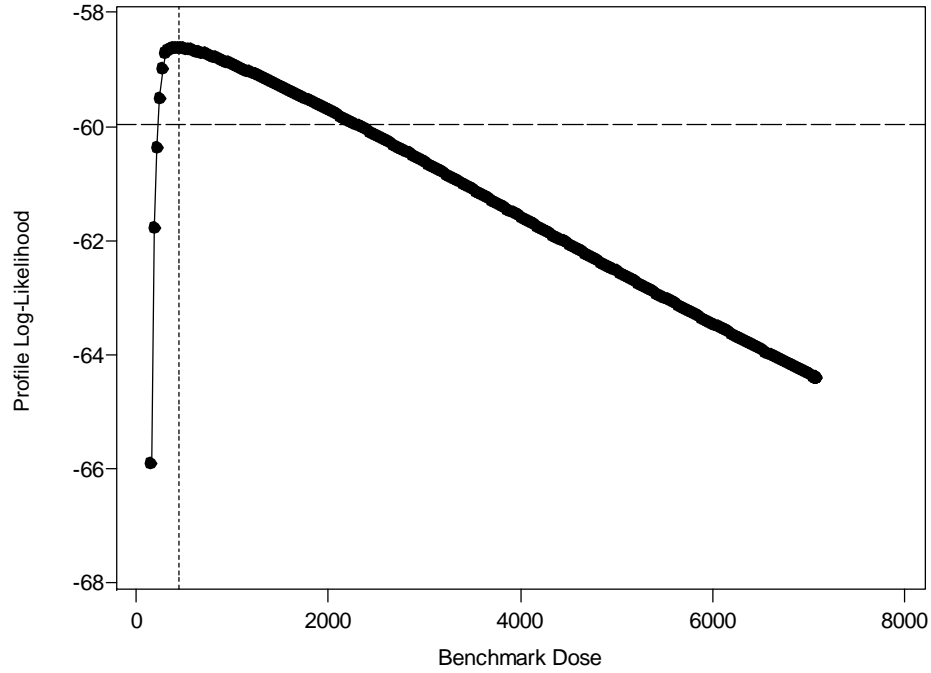
Incidental Extra Risk = 1.0E-04 at 52 Weeks



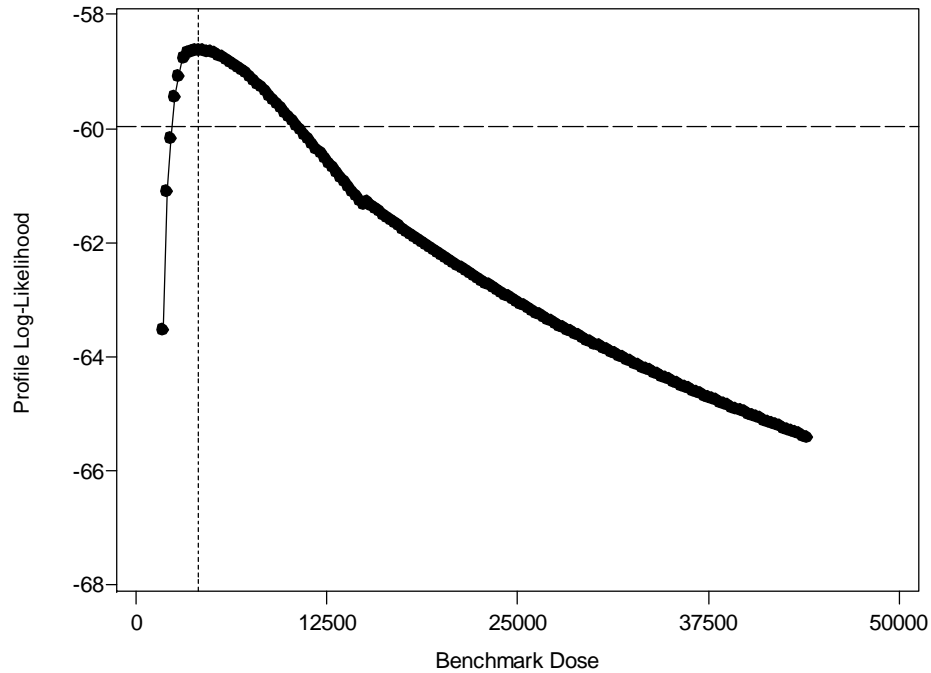
Incidental Extra Risk = 1.0E-03 at 52 Weeks



Incidental Extra Risk = 1.0E-02 at 52 Weeks



Incidental Extra Risk = 1.0E-01 at 52 Weeks



A3.2. 1-Stage Model, Fixed $t_0 = 0$

A3.2.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-5.867227E+001	2.709143E+000	0	0.000000E+000
BMDS	-5.867227E+001	2.709143E+000	0	0.000000E+000

Software	Parameter MLE
	β_1
TOXRISK	7.001441E-007
BMDS	7.001423E-007

A3.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

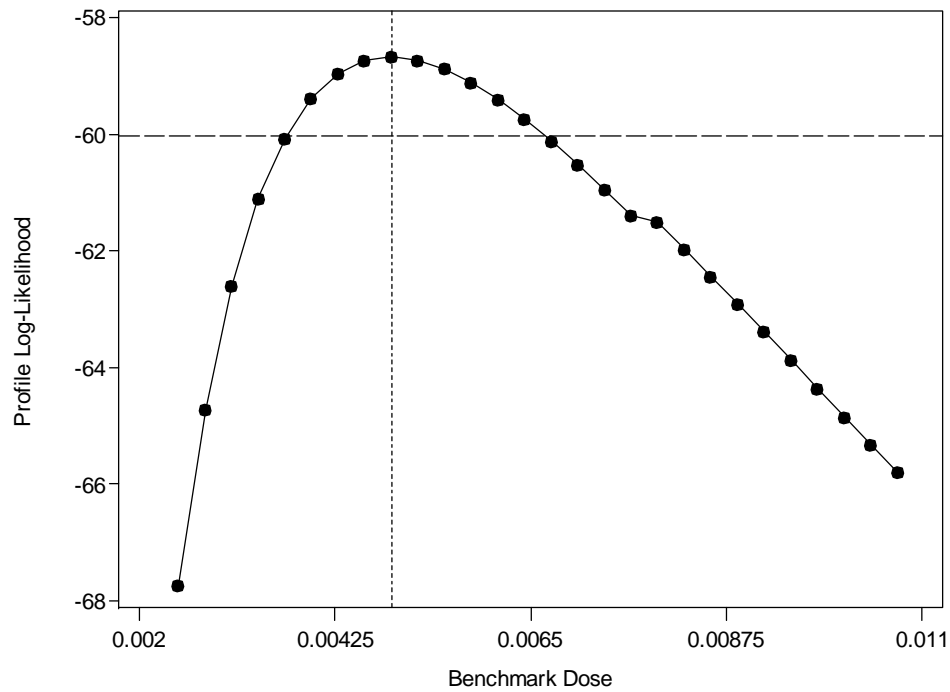
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	3.2411E-003	4.9021E-003	7.6233E-003
	BMDS	3.6919E-003	4.9021E-003	6.6737E-003
1.0E-05	TOXRISK	3.2411E-002	4.9021E-002	7.6307E-002
	BMDS	3.6886E-002	4.9021E-002	7.0078E-002
1.0E-04	TOXRISK	3.2413E-001	4.9023E-001	7.6299E-001
	BMDS	3.4664E-001	4.9023E-001	6.7016E-001
1.0E-03	TOXRISK	3.2427E+000	4.9045E+000	7.6333E+000
	BMDS	3.4836E+000	4.9045E+000	6.7219E+000
1.0E-02	TOXRISK	3.2574E+001	4.9268E+001	7.6679E+001
	BMDS	3.4907E+001	4.9268E+001	7.0293E+001
1.0E-01	TOXRISK	3.4148E+002	5.1649E+002	8.0385E+002
	BMDS	3.6520E+002	5.1649E+002	7.5020E+002

Incidental Extra Risk at 52 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	1.5952E-002	3.2056E-002	7.1821E-002
	BMDS	2.4551E-002	3.2056E-002	9.1884E-002

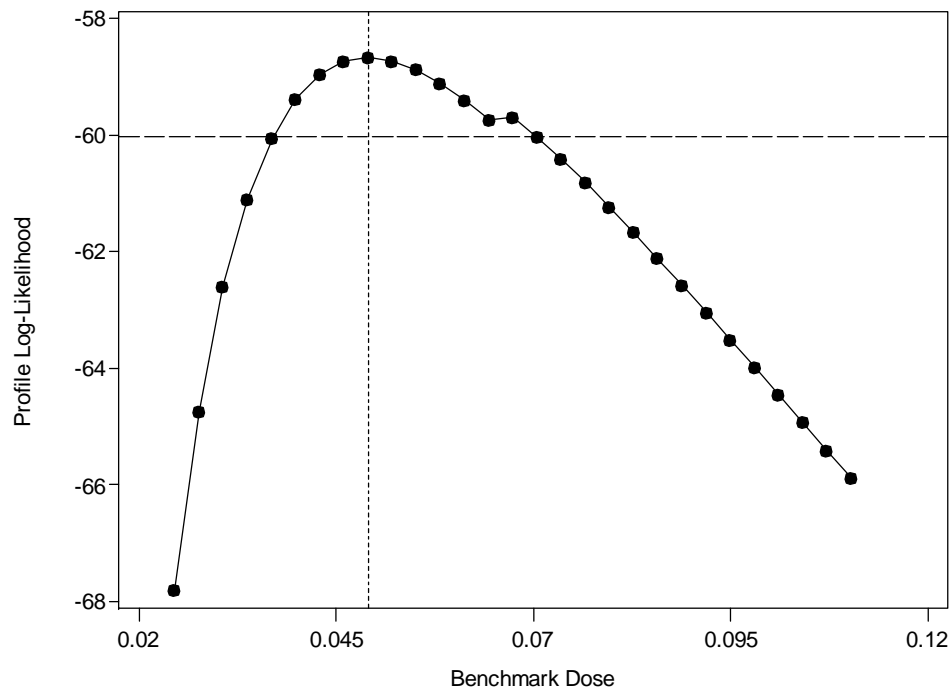
1.0E-05	TOXRISK	1.5953E-001	3.2057E-001	7.1796E-001
	BMDS	2.2136E-001	3.2057E-001	9.1885E-001
1.0E-04	TOXRISK	1.5953E+000	3.2058E+000	7.1799E+000
	BMDS	2.4936E+000	3.2058E+000	9.1889E+000
1.0E-03	TOXRISK	1.5960E+001	3.2072E+001	7.1832E+001
	BMDS	2.5000E+001	3.2072E+001	9.1930E+001
1.0E-02	TOXRISK	1.6033E+002	3.2218E+002	7.2157E+002
	BMDS	2.2284E+002	3.2218E+002	9.2347E+002
1.0E-01	TOXRISK	1.6808E+003	3.3775E+003	7.5644E+003
	BMDS	2.4475E+003	3.3775E+003	9.6810E+003

A3.2.3. Plots of Profile Log-Likelihood Functions

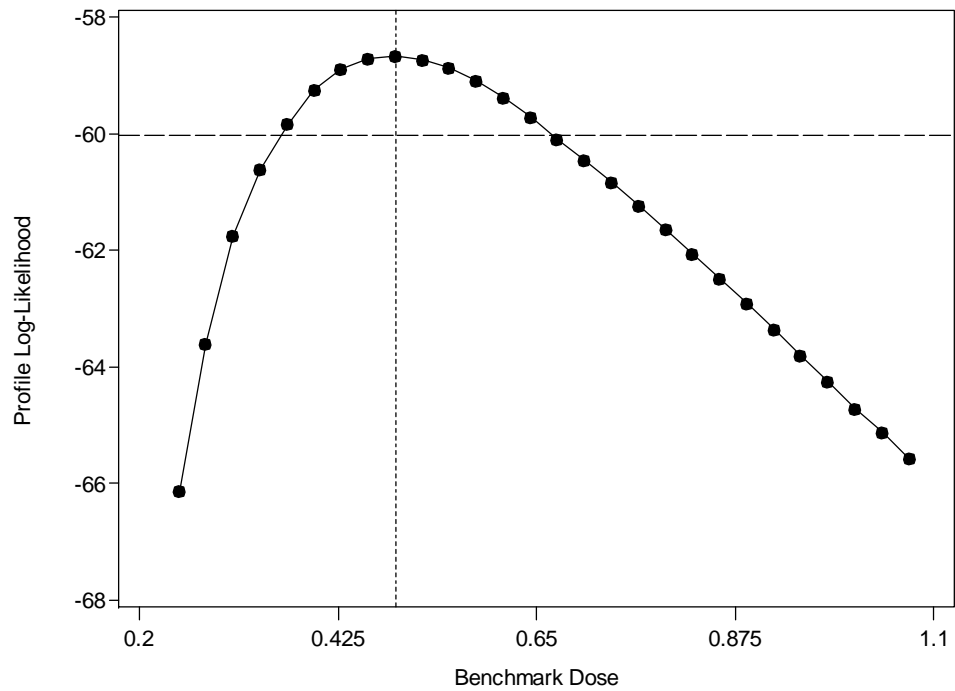
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



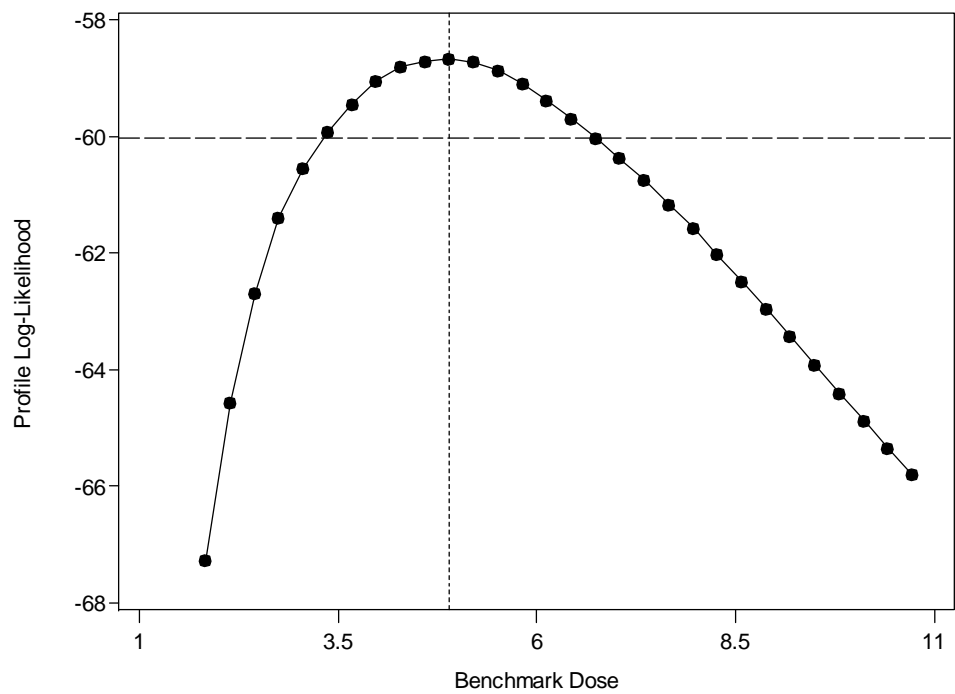
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



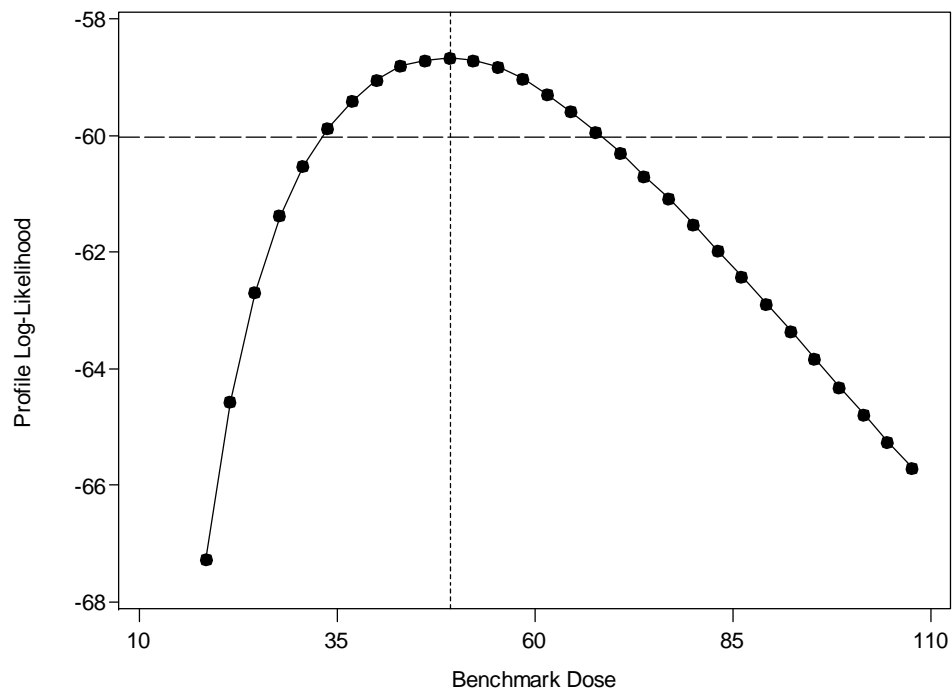
Incidental Extra Risk = $1.0\text{E-}04$ at 104 Weeks



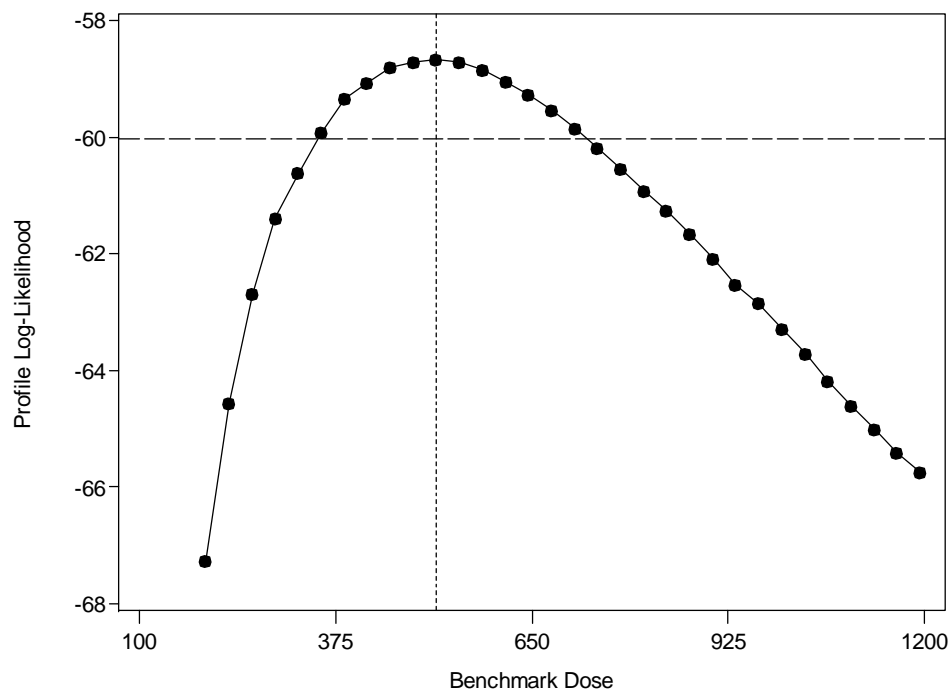
Incidental Extra Risk = $1.0\text{E-}03$ at 104 Weeks



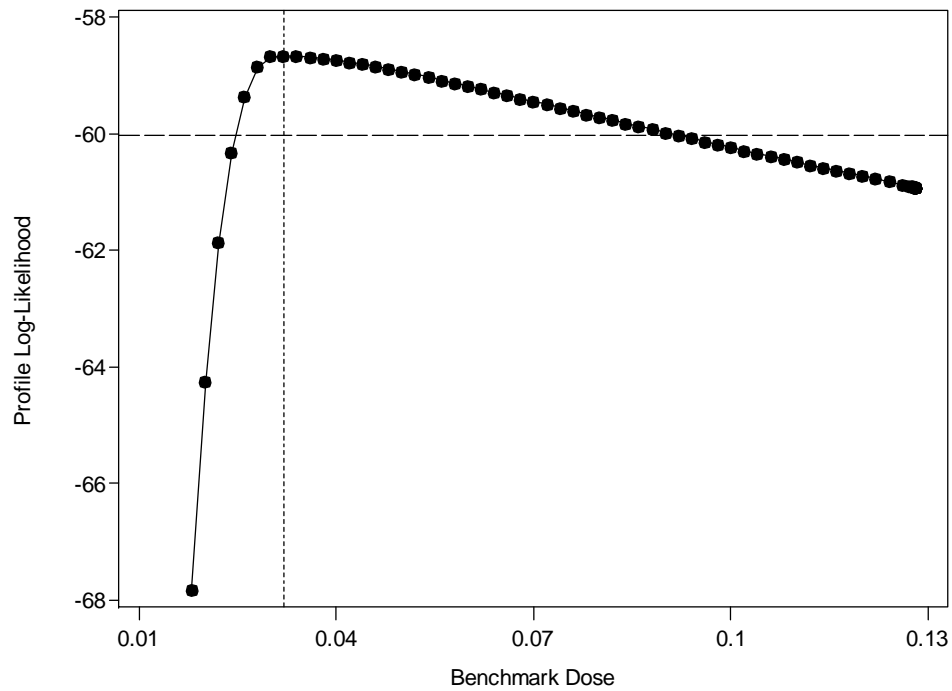
Incidental Extra Risk = 1.0E-02 at 104 Weeks



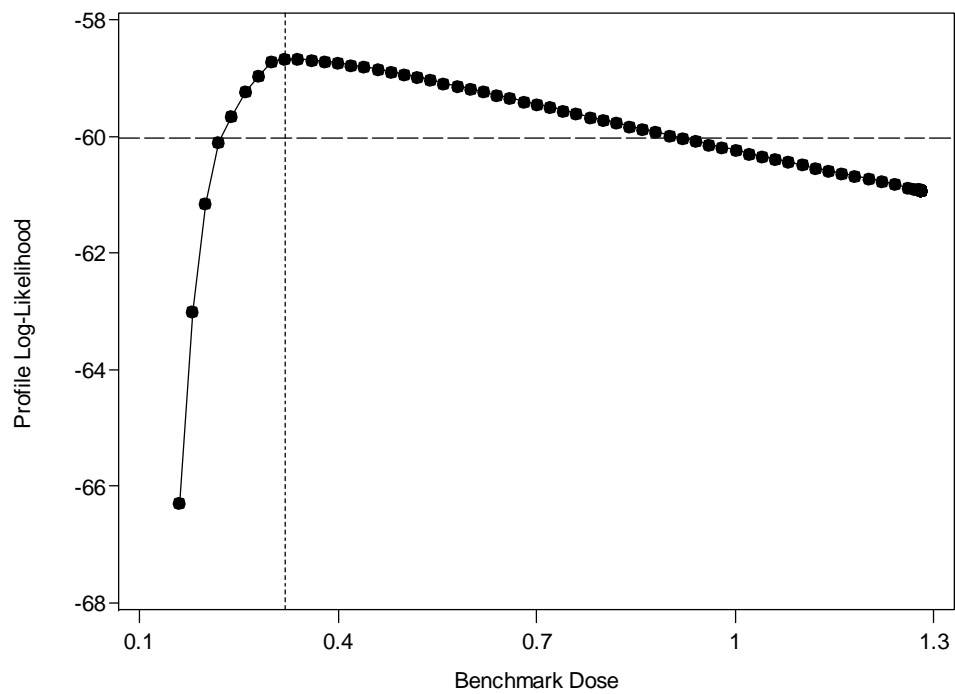
Incidental Extra Risk = 1.0E-01 at 104 Weeks



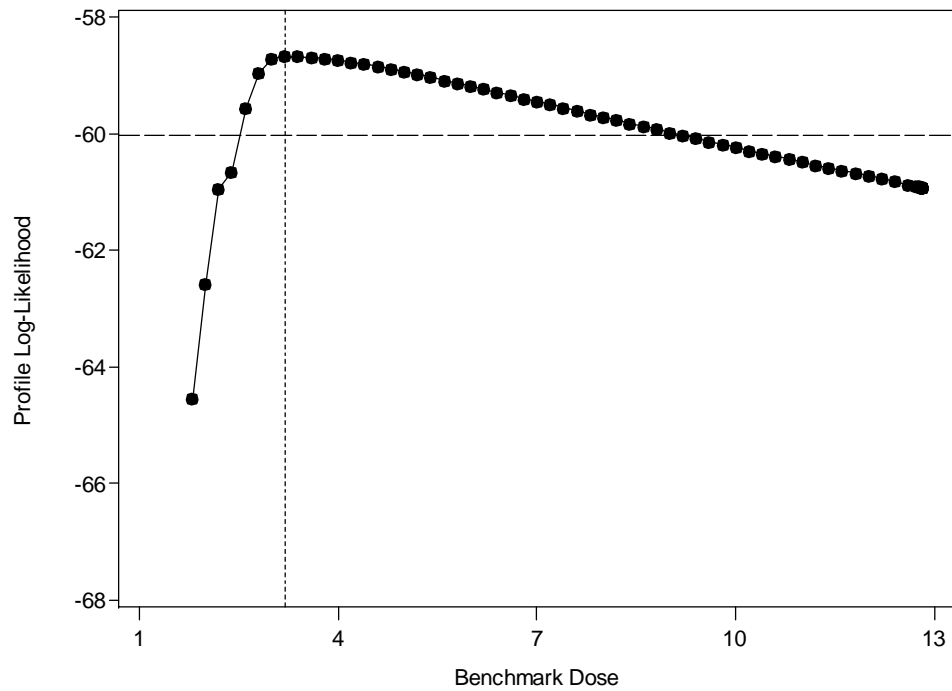
Incidental Extra Risk = 1.0E-06 at 52 Weeks



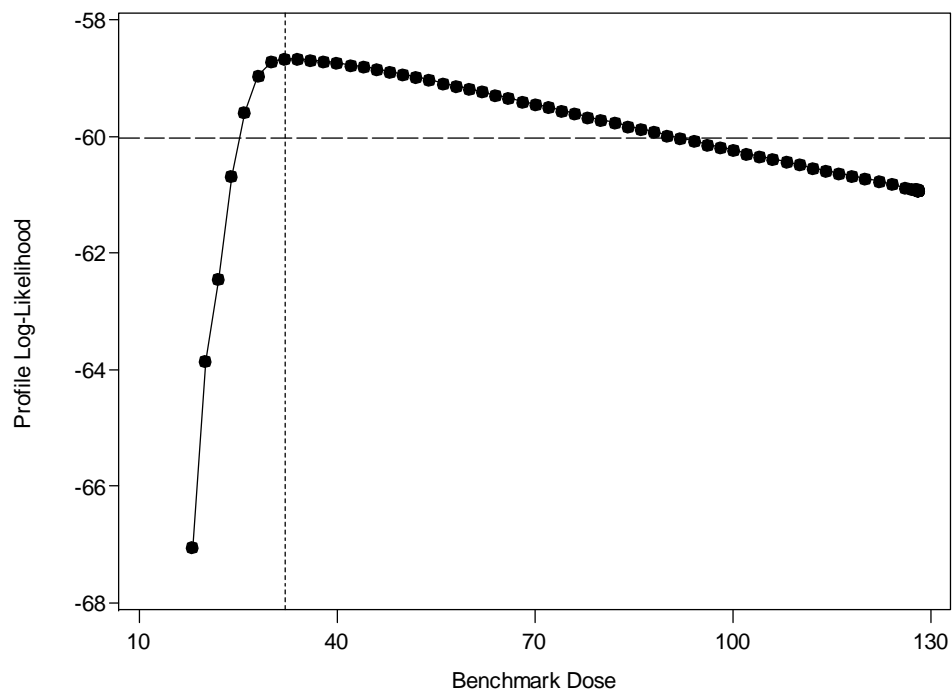
Incidental Extra Risk = 1.0E-05 at 52 Weeks



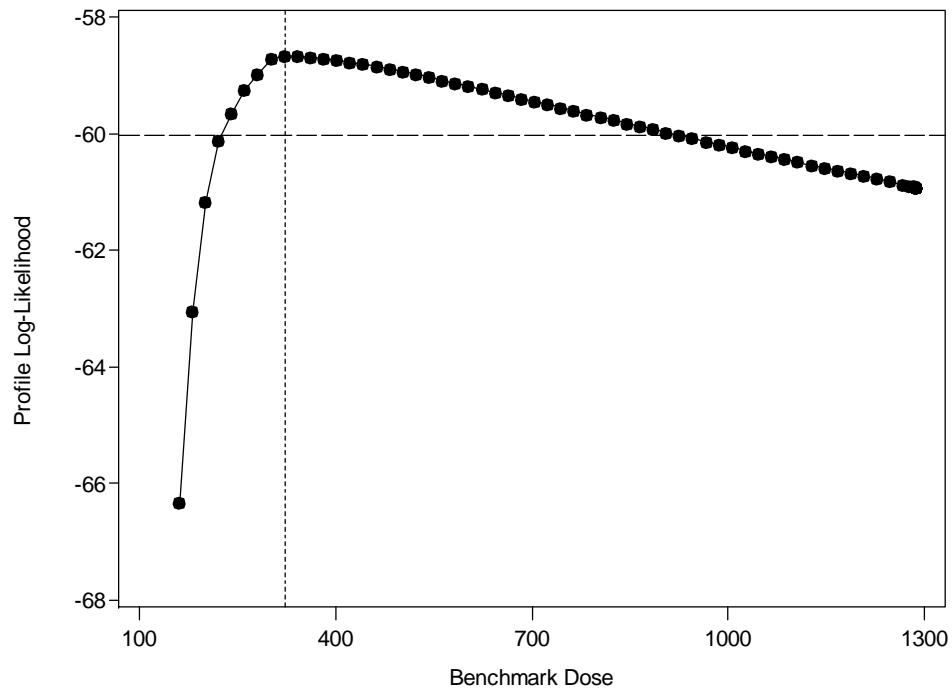
Incidental Extra Risk = 1.0E-04 at 52 Weeks



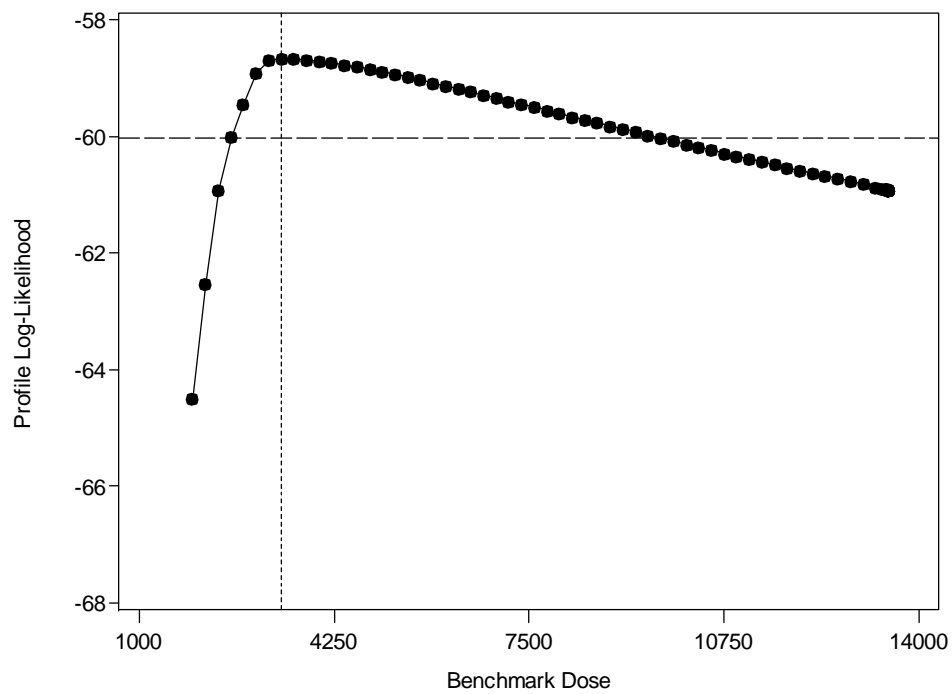
Incidental Extra Risk = 1.0E-03 at 52 Weeks



Incidental Extra Risk = 1.0E-02 at 52 Weeks



Incidental Extra Risk = 1.0E-01 at 52 Weeks



A4. Simulated Dataset 1 (sim11jun07a)

A4.1. 3-Stage Model, Fixed $t_0 = 9$

A4.1.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.187428E+002	7.440749E+000	9	0.000000E+000
BMDS	-2.187428E+002	7.440749E+000	9	0.000000E+000

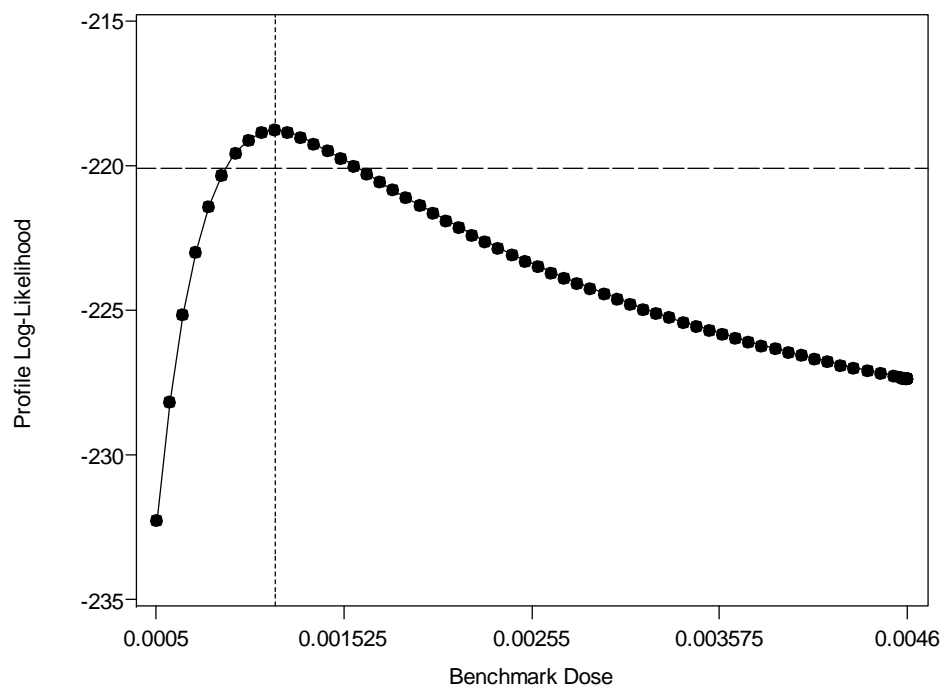
Software	Parameter MLE		
	β_1	β_2	β_3
TOXRISK	8.536165E-016	0.000000E+000	0.000000E+000
BMDS	8.536160E-016	0.000000E+000	0.000000E+000

A4.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

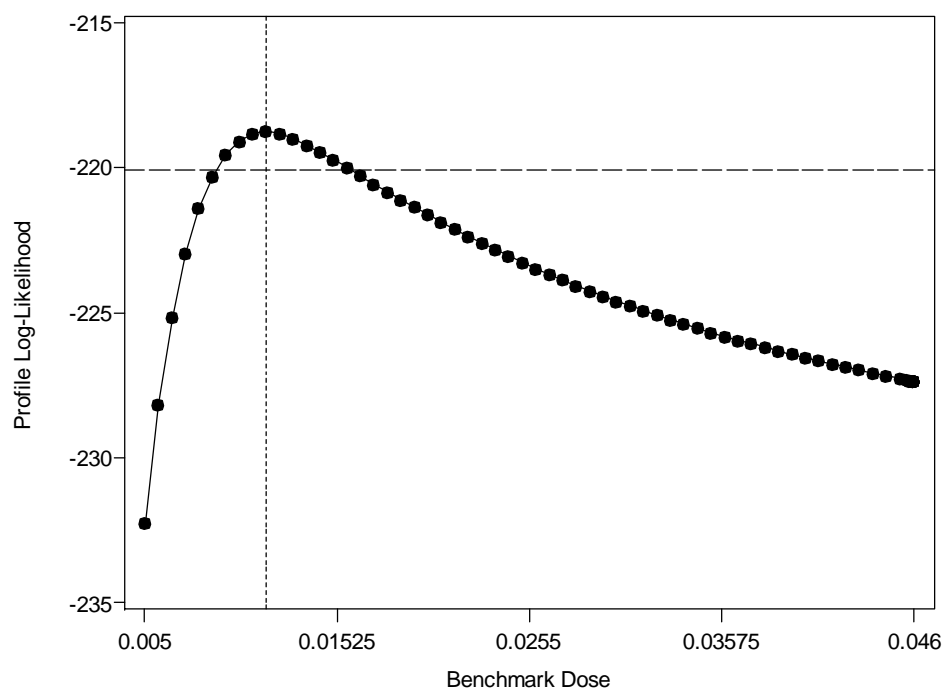
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	8.7879E-004	1.1495E-003	1.6287E-003
	BMDS	8.3542E-004	1.1495E-003	1.7531E-003
1.0E-05	TOXRISK	8.7879E-003	1.1495E-002	1.6049E-002
	BMDS	8.3542E-003	1.1495E-002	1.7531E-002
1.0E-04	TOXRISK	8.7883E-002	1.1495E-001	1.6040E-001
	BMDS	8.3546E-002	1.1495E-001	1.7532E-001
1.0E-03	TOXRISK	8.7923E-001	1.1500E+000	1.6045E+000
	BMDS	8.3593E-001	1.1500E+000	1.7538E+000
1.0E-02	TOXRISK	8.8321E+000	1.1553E+001	1.6107E+001
	BMDS	8.3962E+000	1.1553E+001	1.7599E+001
1.0E-01	TOXRISK	9.2590E+001	1.2111E+002	1.6776E+002
	BMDS	8.8020E+001	1.2111E+002	1.8254E+002

A4.1.3. Plots of Profile Log-Likelihood Functions

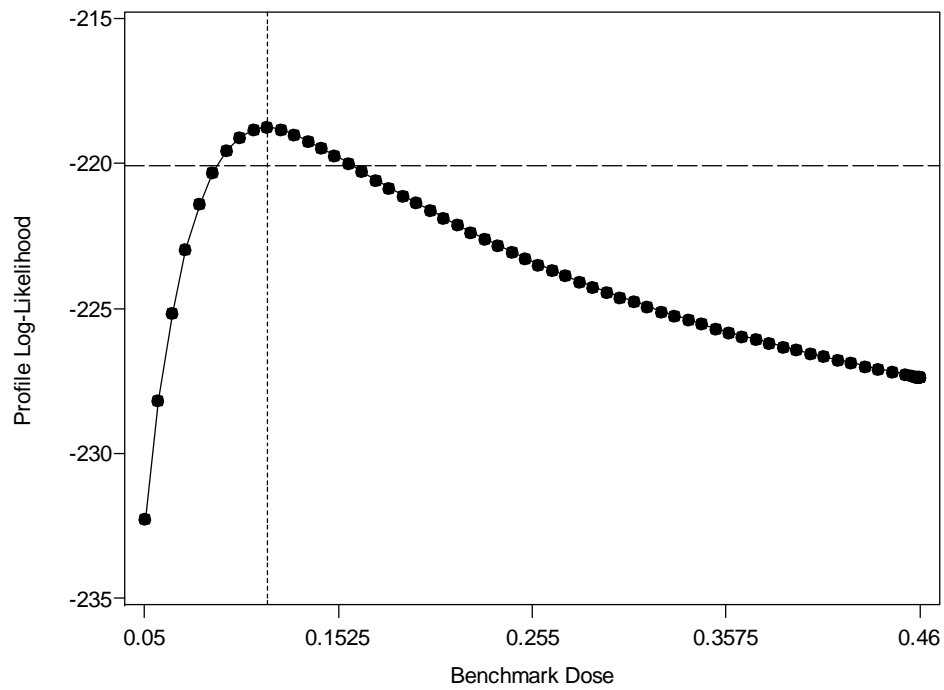
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



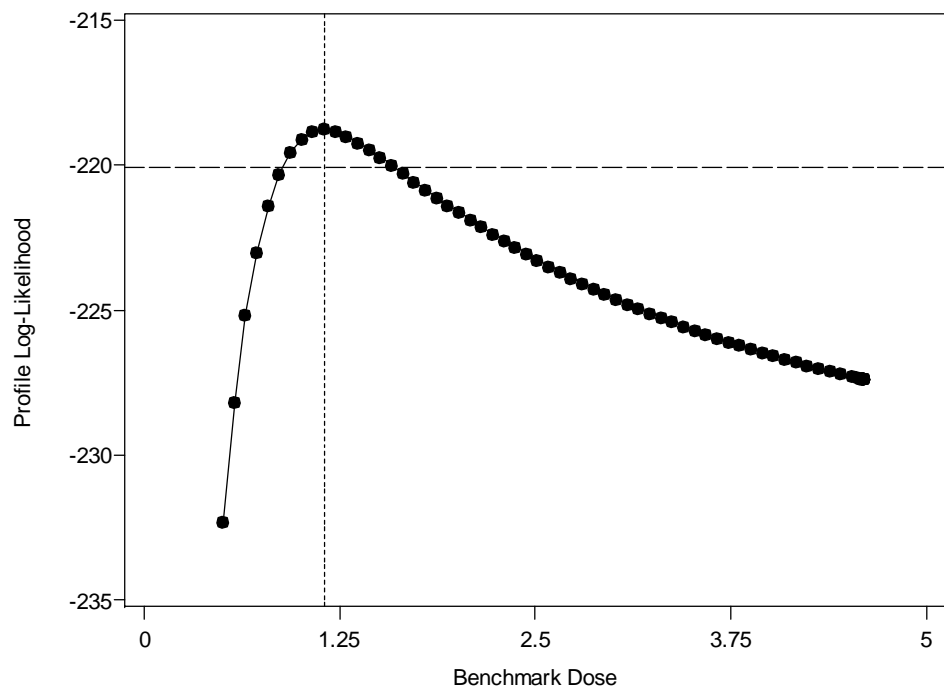
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



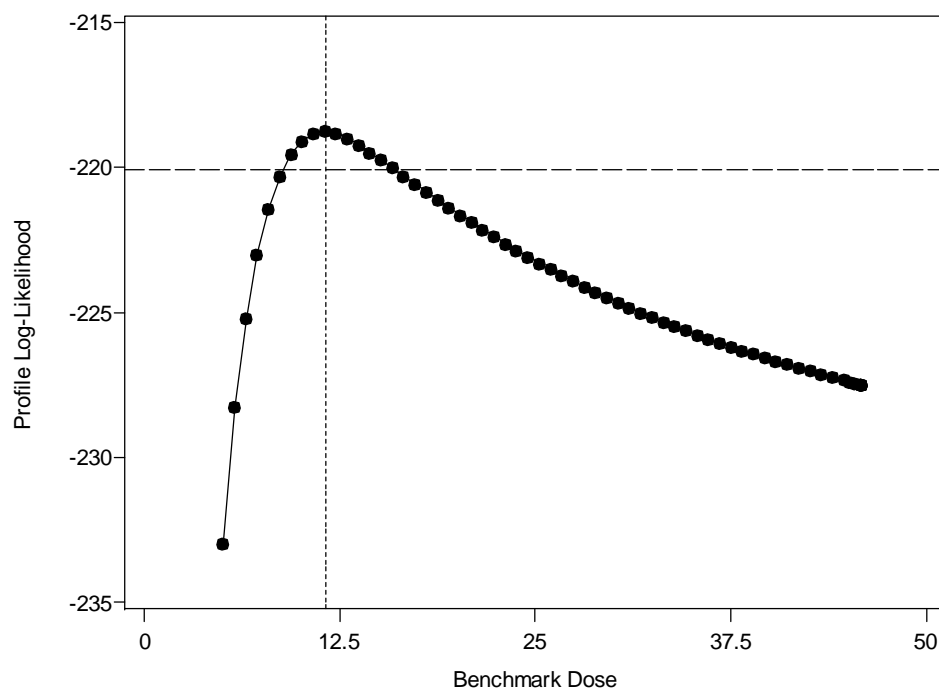
Incidental Extra Risk = 1.0E-04 at 104 Weeks



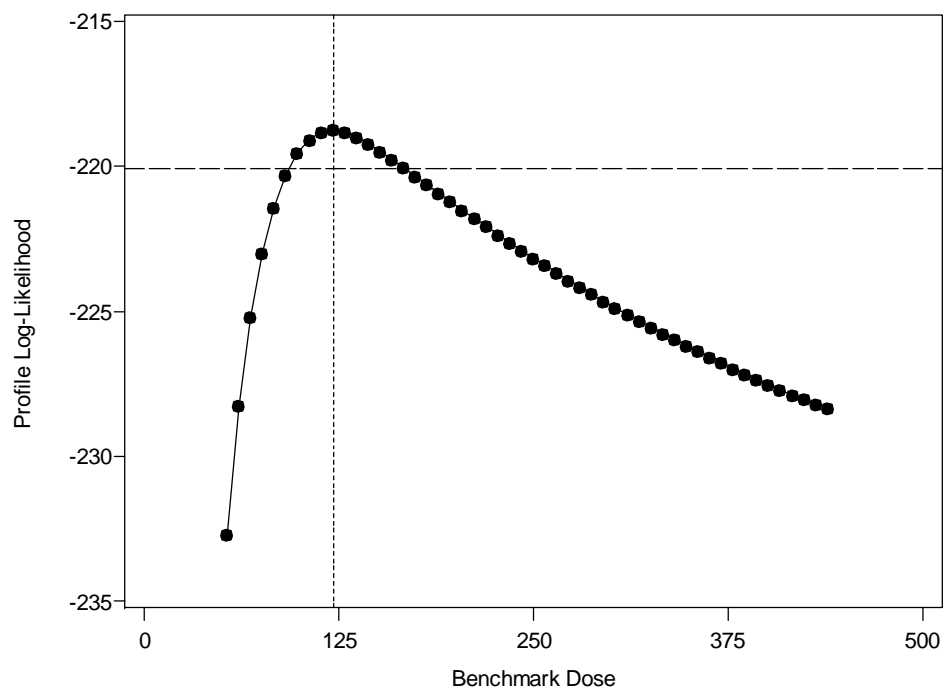
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A4.2. 3-Stage Model, Fixed $t_0 = 19$

A4.2.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.147580E+002	5.789571E+000	19	0.000000E+000
BMDS	-2.147580E+002	5.789571E+000	19	0.000000E+000

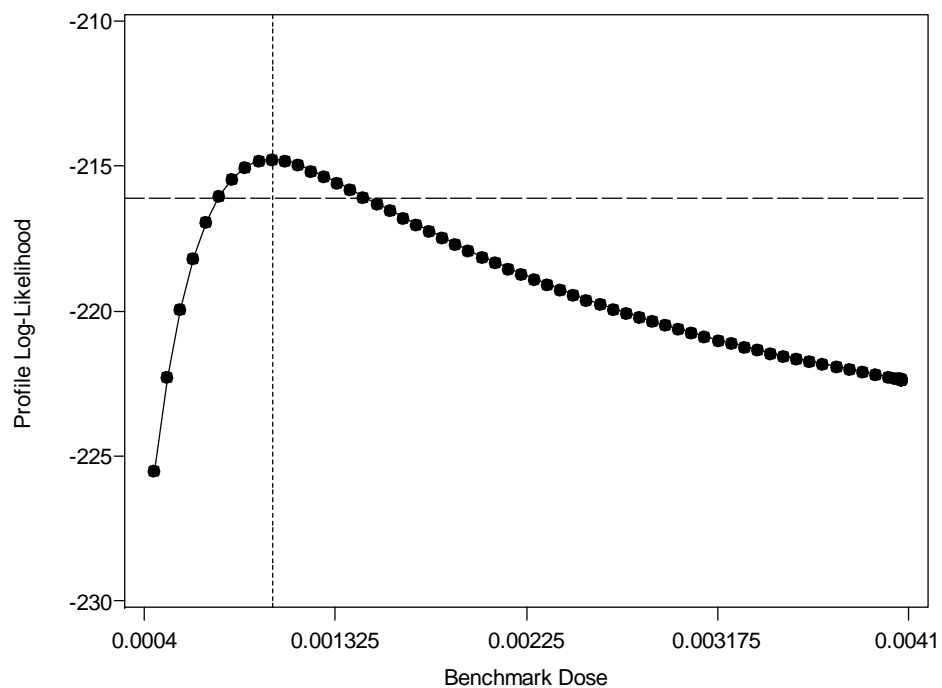
Software	Parameter MLE		
	β_1	β_2	β_3
TOXRISK	2.063400E-012	0.000000E+000	0.000000E+000
BMDS	2.063400E-012	0.000000E+000	0.000000E+000

A4.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

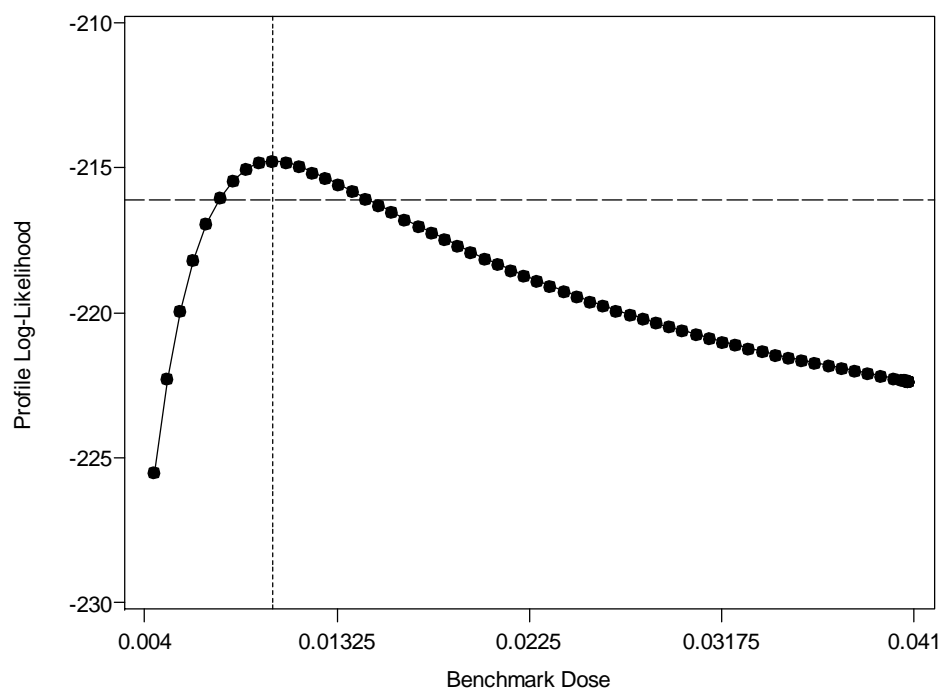
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	7.5689E-004	1.0178E-003	1.4727E-003
	BMDS	7.1545E-004	1.0178E-003	1.6301E-003
1.0E-05	TOXRISK	7.5690E-003	1.0178E-002	1.4816E-002
	BMDS	7.1546E-003	1.0178E-002	1.6301E-002
1.0E-04	TOXRISK	7.5693E-002	1.0178E-001	1.4799E-001
	BMDS	7.1549E-002	1.0178E-001	1.6301E-001
1.0E-03	TOXRISK	7.5727E-001	1.0183E+000	1.4803E+000
	BMDS	7.1583E-001	1.0183E+000	1.6307E+000
1.0E-02	TOXRISK	7.6070E+000	1.0229E+001	1.4859E+001
	BMDS	7.1905E+000	1.0229E+001	1.6360E+001
1.0E-01	TOXRISK	7.9747E+001	1.0723E+002	1.5456E+002
	BMDS	7.5380E+001	1.0723E+002	1.6938E+002

A4.2.3. Plots of Profile Log-Likelihood Functions

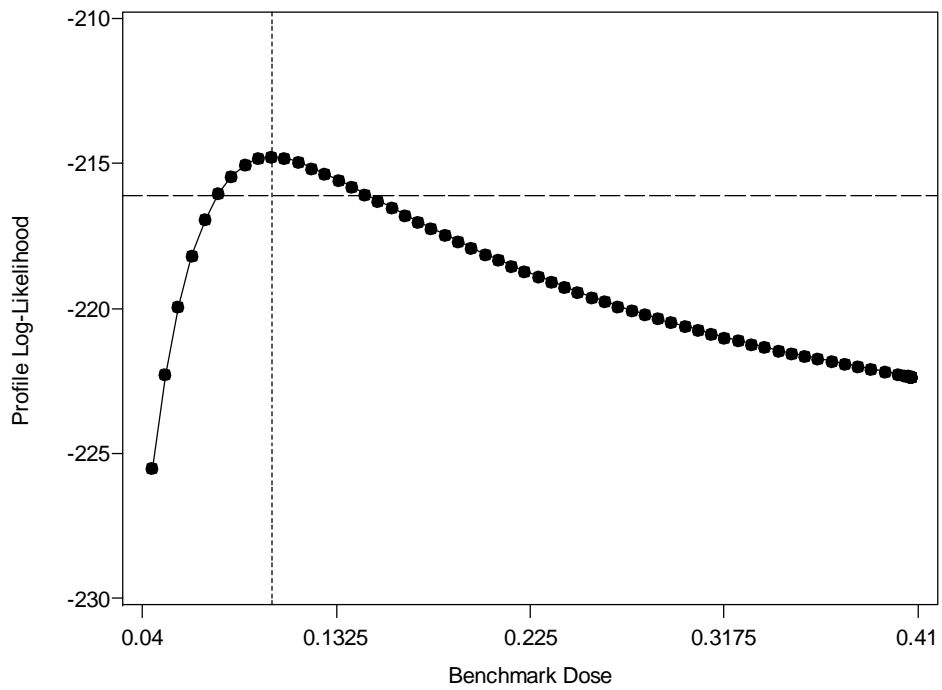
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



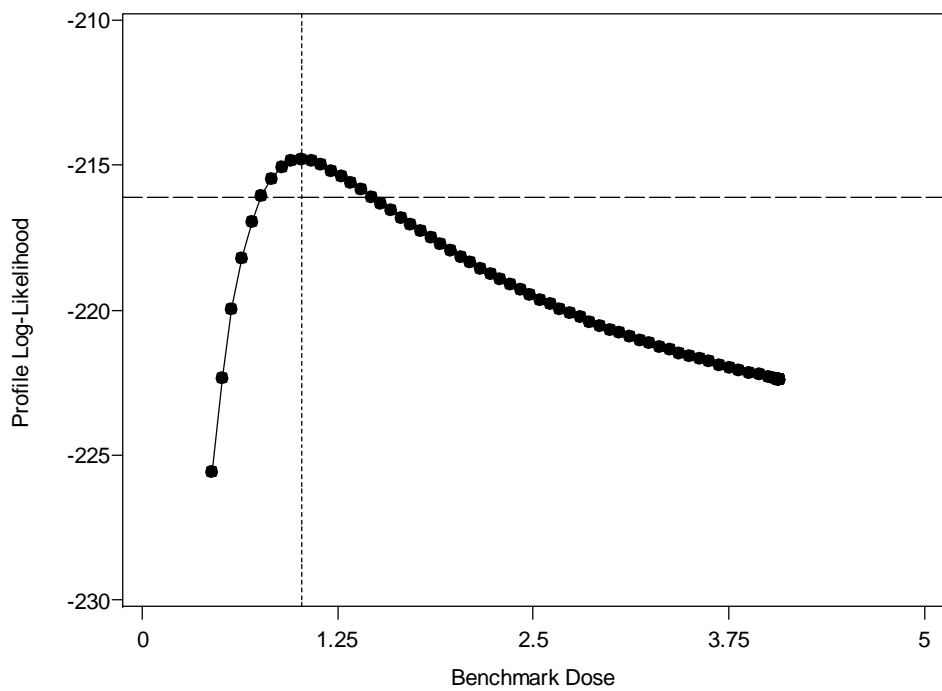
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



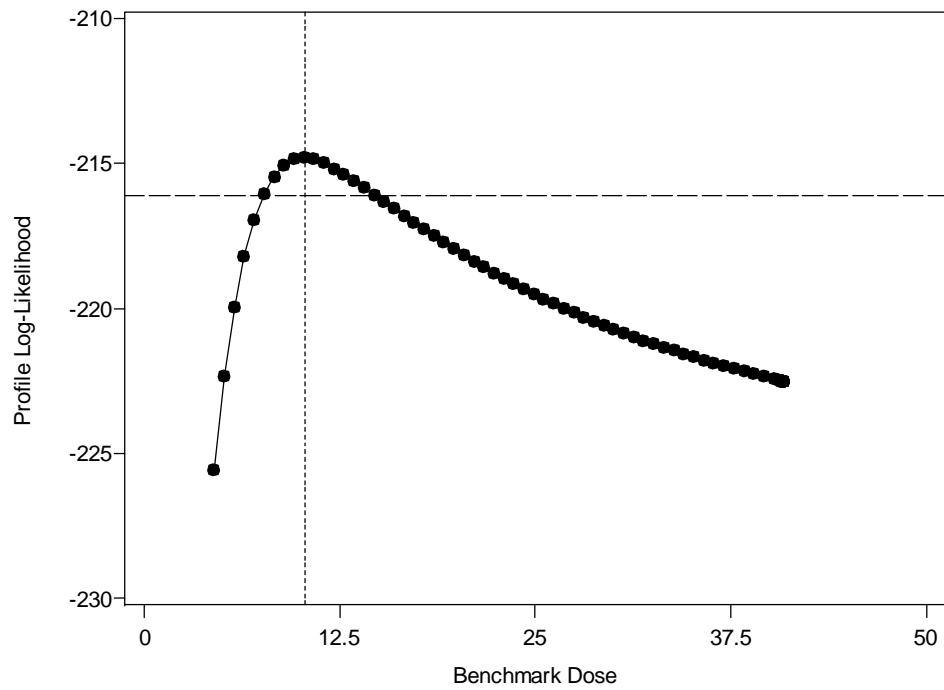
Incidental Extra Risk = 1.0E-04 at 104 Weeks



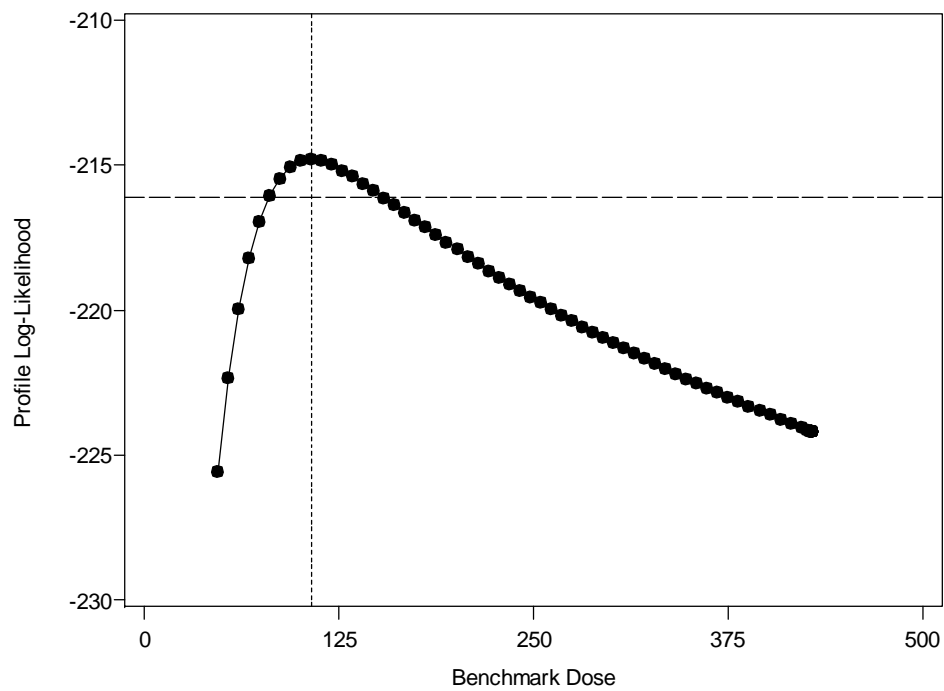
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A4.3. 2-Stage Model, Fixed $t_0 = 9$

A4.3.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.187428E+002	7.440749E+000	9	0.000000E+000
BMDs	-2.187428E+002	7.440749E+000	9	0.000000E+000

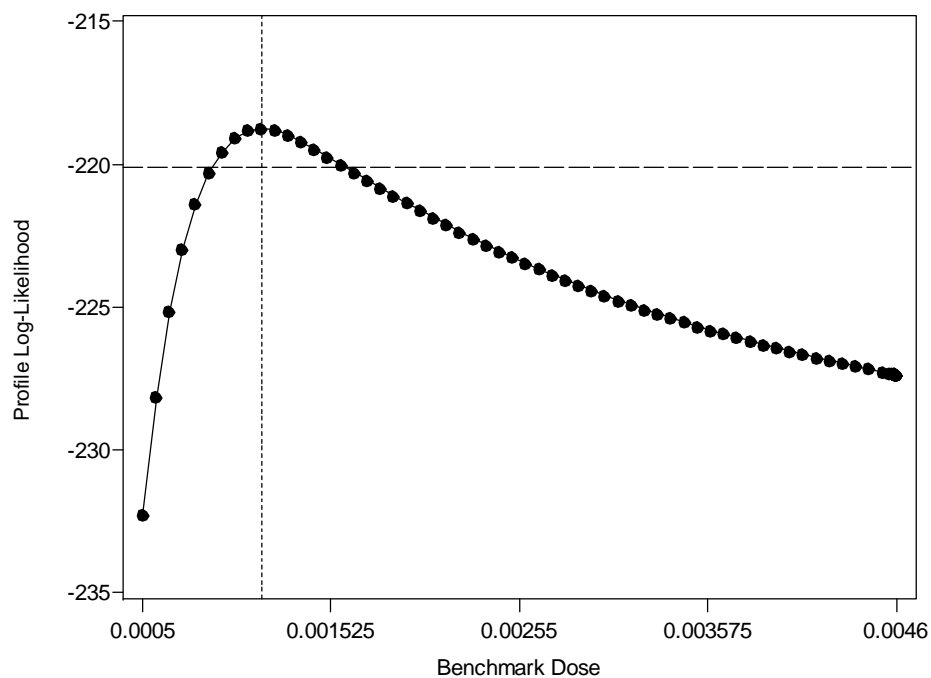
Software	Parameter MLE	
	β_1	β_2
TOXRISK	8.536165E-016	0.000000E+000
BMDs	8.536164E-016	0.000000E+000

A4.3.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

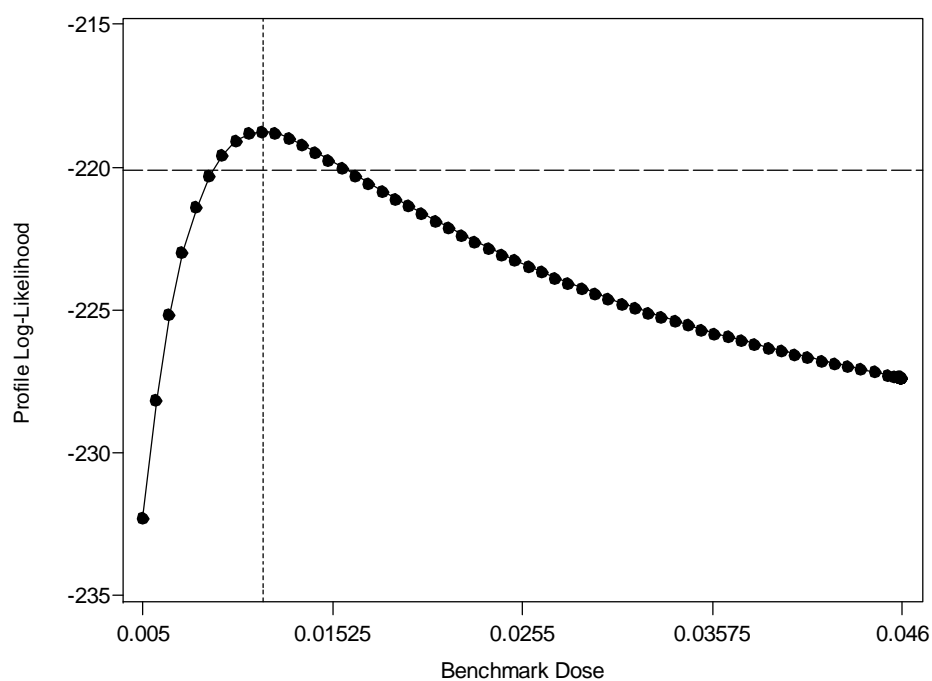
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	8.7879E-004	1.1495E-003	1.6287E-003
	BMDs	8.3542E-004	1.1495E-003	1.7531E-003
1.0E-05	TOXRISK	8.7879E-003	1.1495E-002	1.6049E-002
	BMDs	8.3542E-003	1.1495E-002	1.7531E-002
1.0E-04	TOXRISK	8.7883E-002	1.1495E-001	1.6040E-001
	BMDs	8.3546E-002	1.1495E-001	1.7532E-001
1.0E-03	TOXRISK	8.7923E-001	1.1500E+000	1.6045E+000
	BMDs	8.3593E-001	1.1500E+000	1.7538E+000
1.0E-02	TOXRISK	8.8321E+000	1.1553E+001	1.6107E+001
	BMDs	8.3962E+000	1.1553E+001	1.7598E+001
1.0E-01	TOXRISK	9.2590E+001	1.2111E+002	1.6776E+002
	BMDs	8.8020E+001	1.2111E+002	1.8254E+002

A4.3.3. Plots of Profile Log-Likelihood Functions

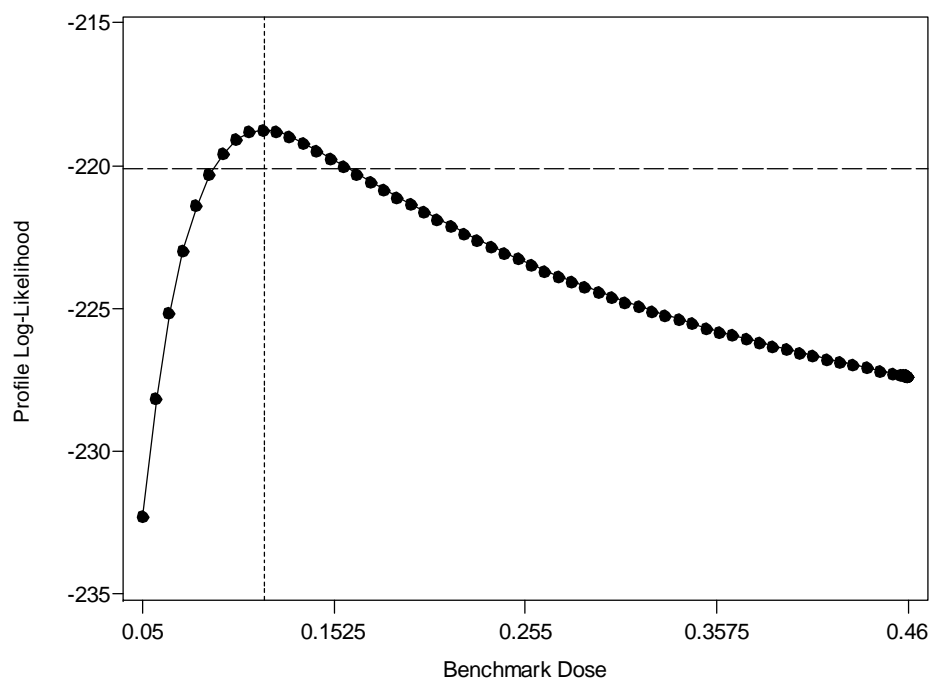
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



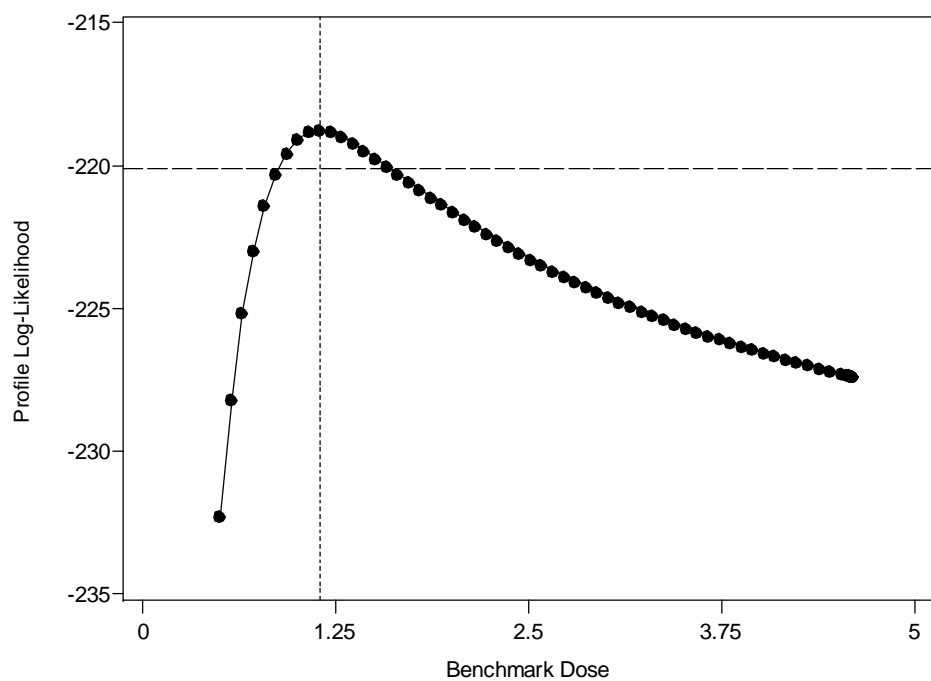
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



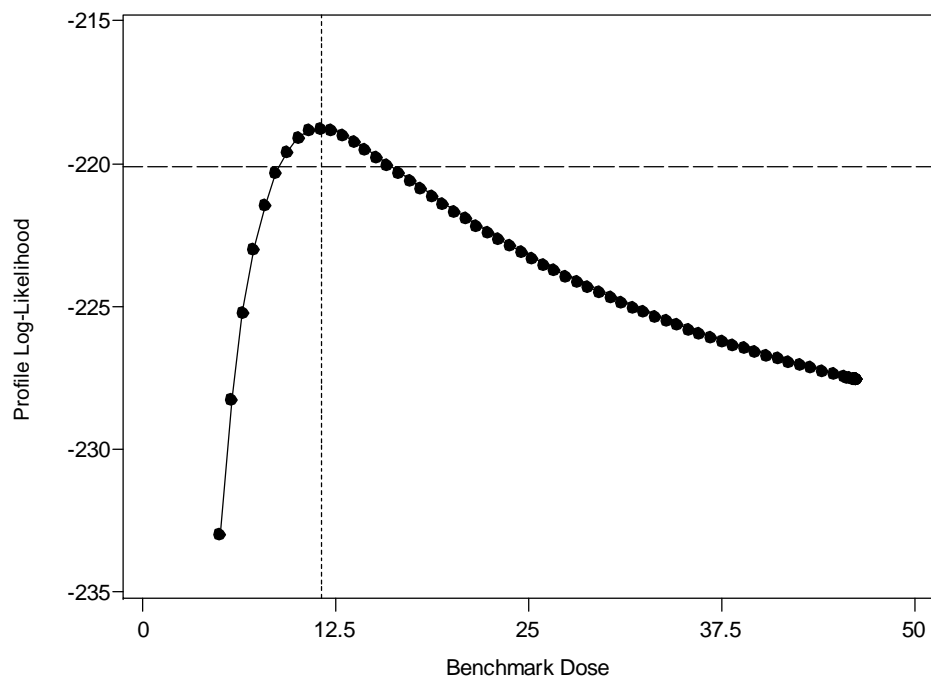
Incidental Extra Risk = 1.0E-04 at 104 Weeks



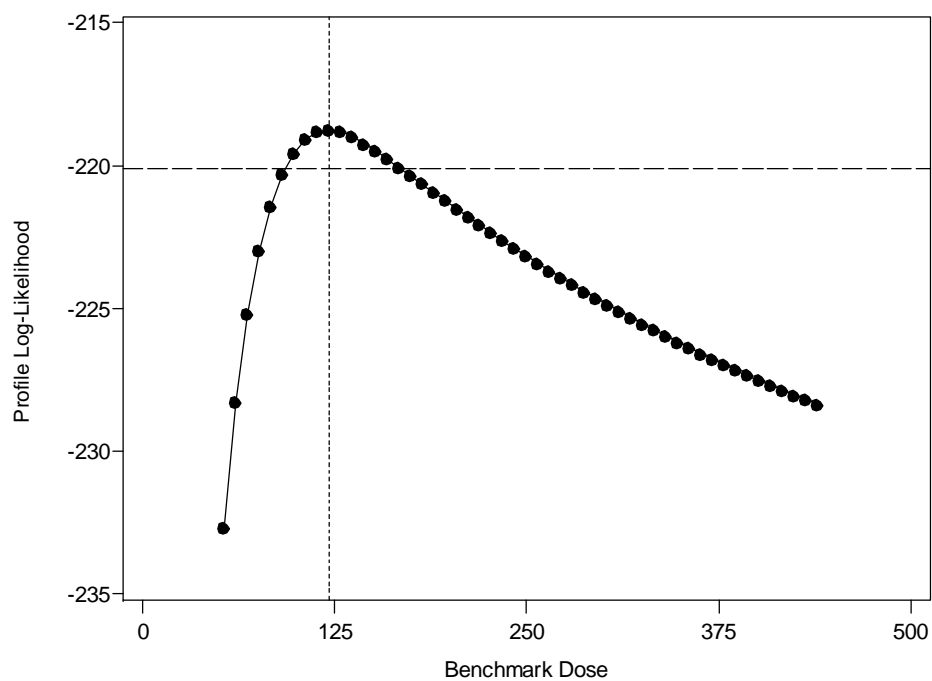
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A4.4. 2-Stage Model, Fixed $t_0 = 19$

A4.4.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.147580E+002	5.789571E+000	19	0.000000E+000
BMDs	-2.147580E+002	5.789571E+000	19	0.000000E+000

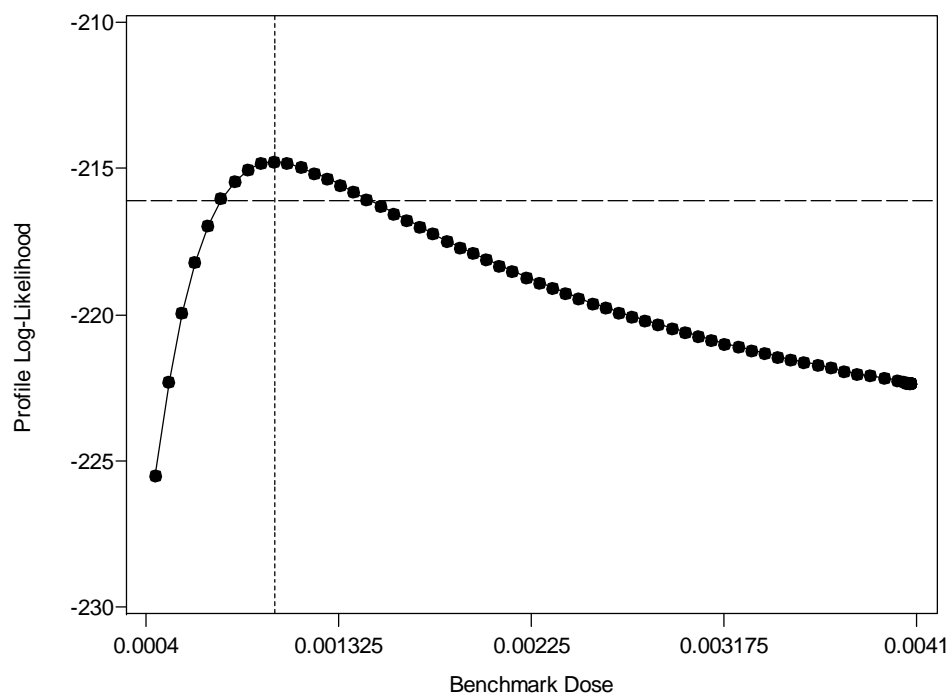
Software	Parameter MLE	
	β_1	β_2
TOXRISK	2.063400E-012	0.000000E+000
BMDs	2.063404E-012	0.000000E+000

A4.4.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

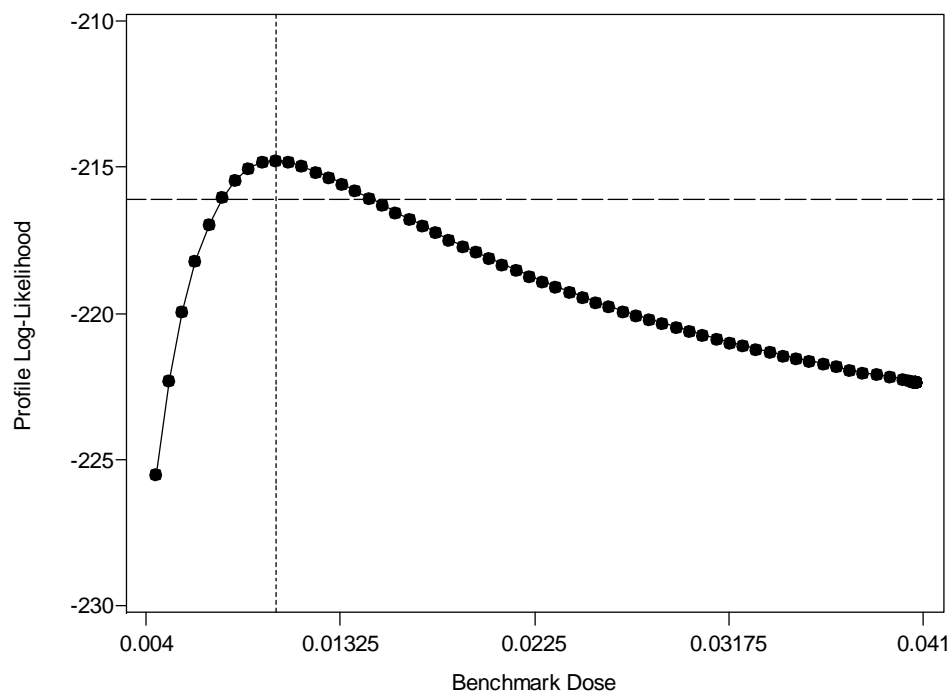
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	7.5689E-004	1.0178E-003	1.4727E-003
	BMDs	7.1545E-004	1.0178E-003	1.6301E-003
1.0E-05	TOXRISK	7.5690E-003	1.0178E-002	1.4816E-002
	BMDs	7.1545E-003	1.0178E-002	1.6301E-002
1.0E-04	TOXRISK	7.5693E-002	1.0178E-001	1.4799E-001
	BMDs	7.1549E-002	1.0178E-001	1.6301E-001
1.0E-03	TOXRISK	7.5727E-001	1.0183E+000	1.4803E+000
	BMDs	7.1583E-001	1.0183E+000	1.6307E+000
1.0E-02	TOXRISK	7.6070E+000	1.0229E+001	1.4859E+001
	BMDs	7.1905E+000	1.0229E+001	1.6360E+001
1.0E-01	TOXRISK	7.9747E+001	1.0723E+002	1.5456E+002
	BMDs	7.5380E+001	1.0723E+002	1.6938E+002

A4.4.3. Plots of Profile Log-Likelihood Functions

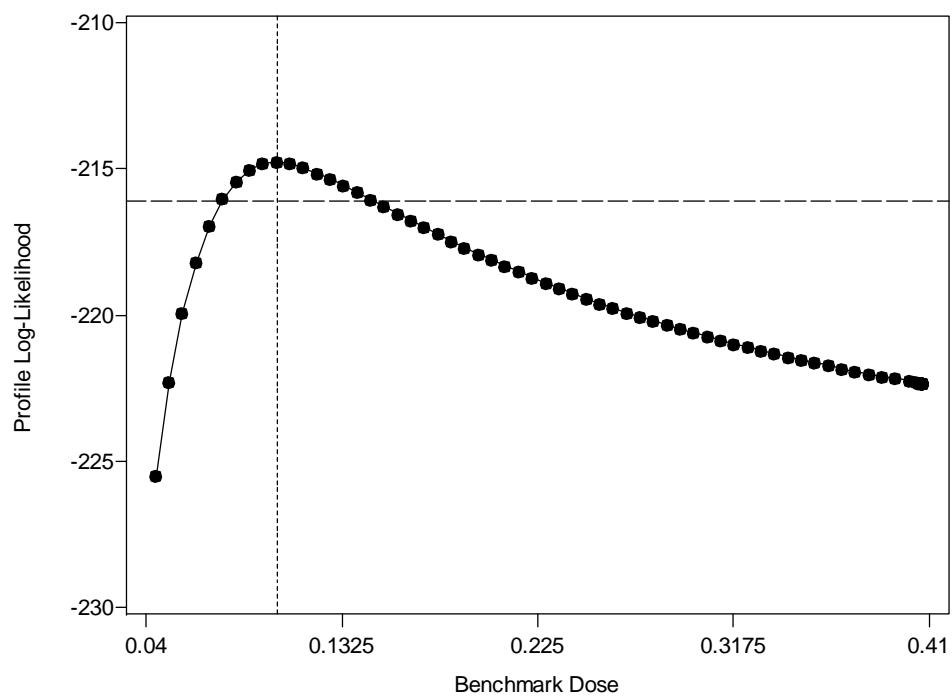
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



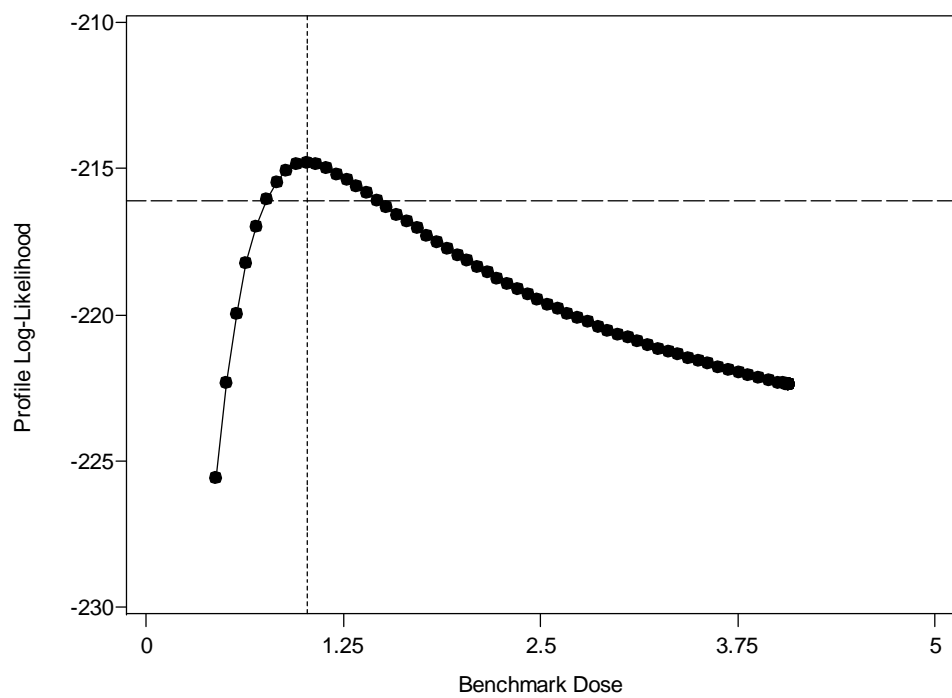
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



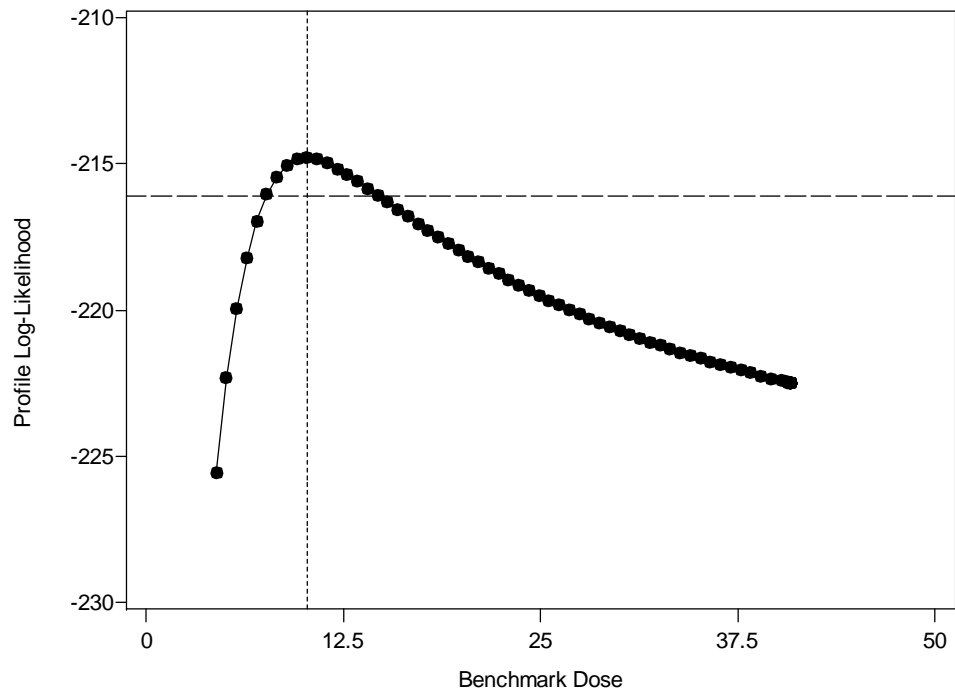
Incidental Extra Risk = 1.0E-04 at 104 Weeks



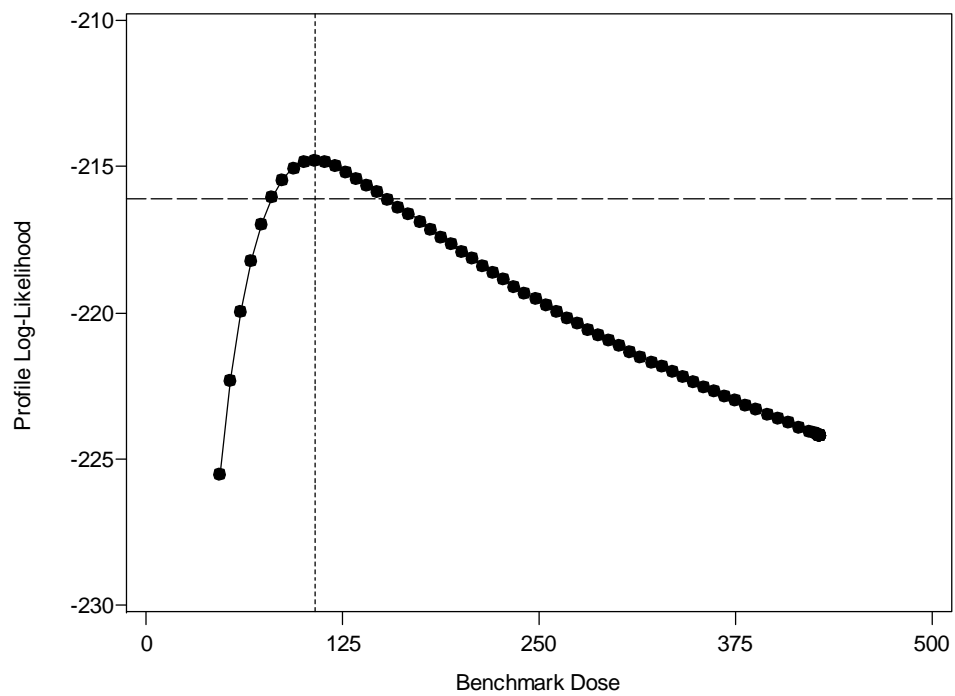
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A4.5. 1-Stage Model, Fixed $t_0 = 9$

A4.5.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.187428E+002	7.440749E+000	9	0.000000E+000
BMDS	-2.187428E+002	7.440748E+000	9	0.000000E+000

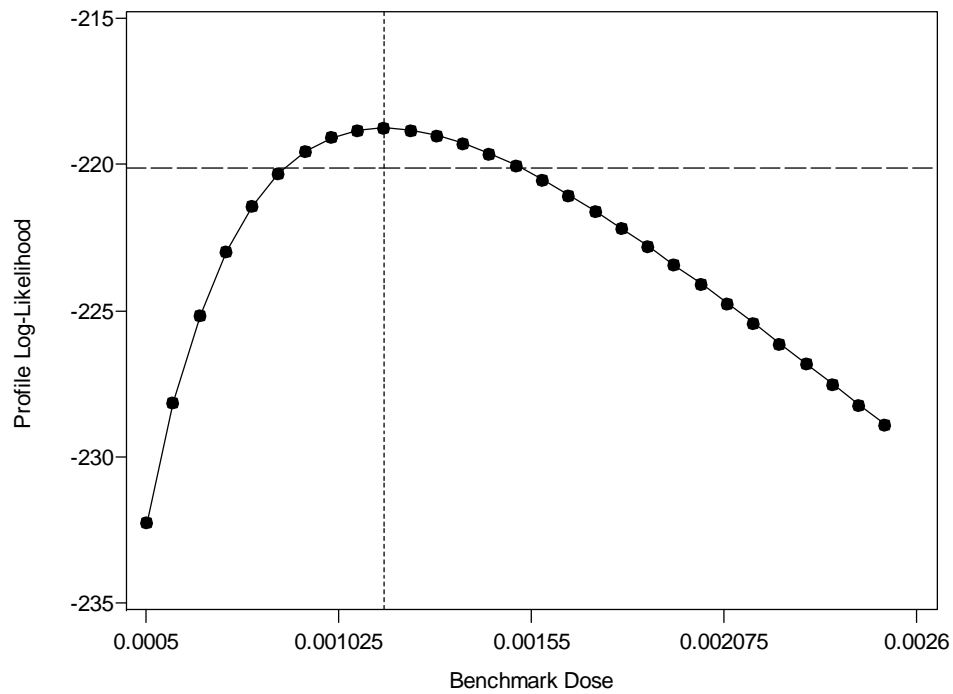
Software	Parameter MLE
	β_1
TOXRISK	8.536165E-016
BMDS	8.536186E-016

A4.5.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

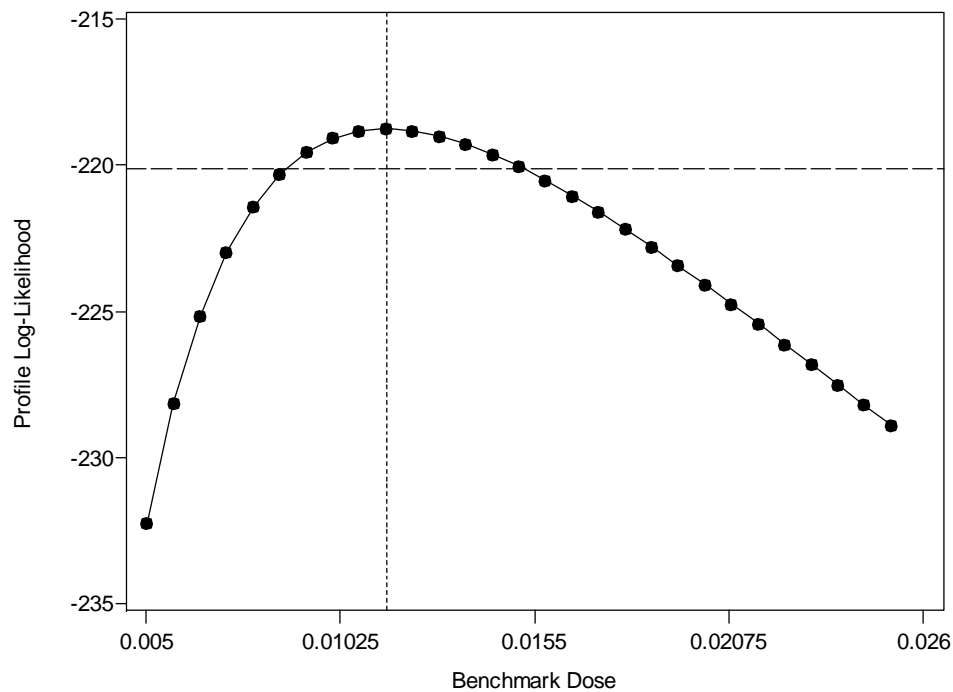
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	8.7879E-004	1.1495E-003	1.5197E-003
	BMDS	8.3542E-004	1.1495E-003	1.6001E-003
1.0E-05	TOXRISK	8.7879E-003	1.1495E-002	1.5155E-002
	BMDS	8.3542E-003	1.1495E-002	1.6002E-002
1.0E-04	TOXRISK	8.7883E-002	1.1495E-001	1.5158E-001
	BMDS	8.3546E-002	1.1495E-001	1.6002E-001
1.0E-03	TOXRISK	8.7923E-001	1.1500E+000	1.5167E+000
	BMDS	8.3593E-001	1.1500E+000	1.6009E+000
1.0E-02	TOXRISK	8.8321E+000	1.1553E+001	1.5236E+001
	BMDS	8.3962E+000	1.1553E+001	1.6082E+001
1.0E-01	TOXRISK	9.2590E+001	1.2111E+002	1.5972E+002
	BMDS	8.8020E+001	1.2111E+002	1.6859E+002

A4.5.3. Plots of Profile Log-Likelihood Functions

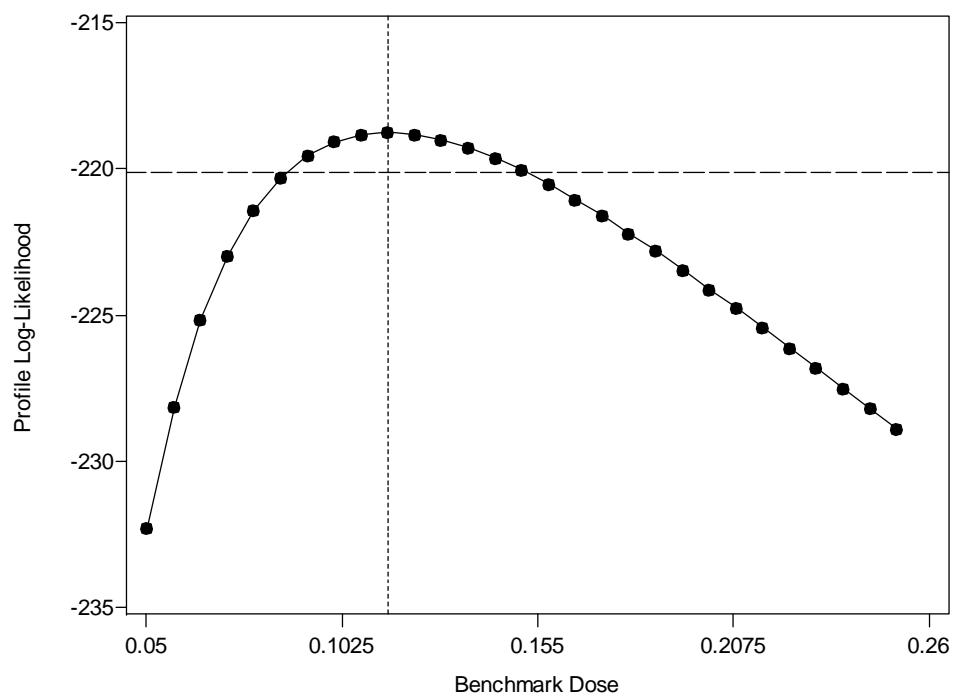
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



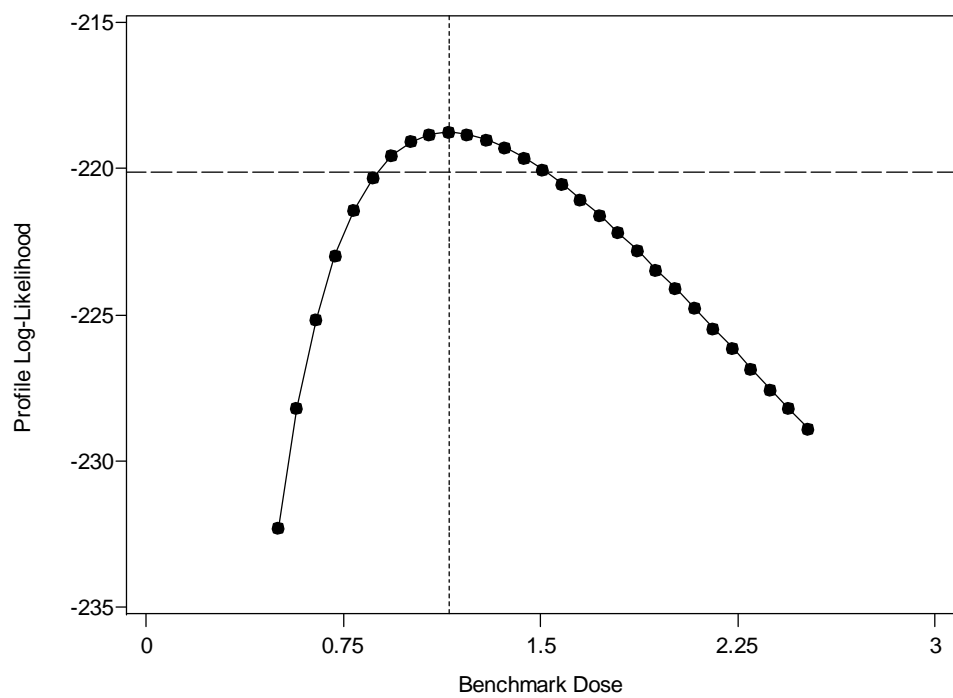
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



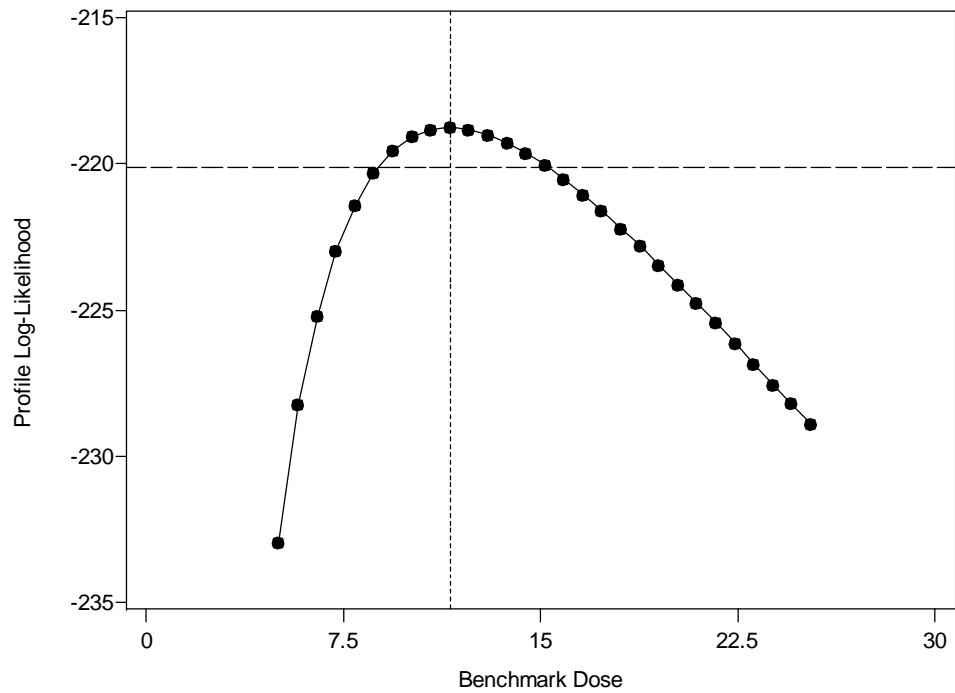
Incidental Extra Risk = 1.0E-04 at 104 Weeks



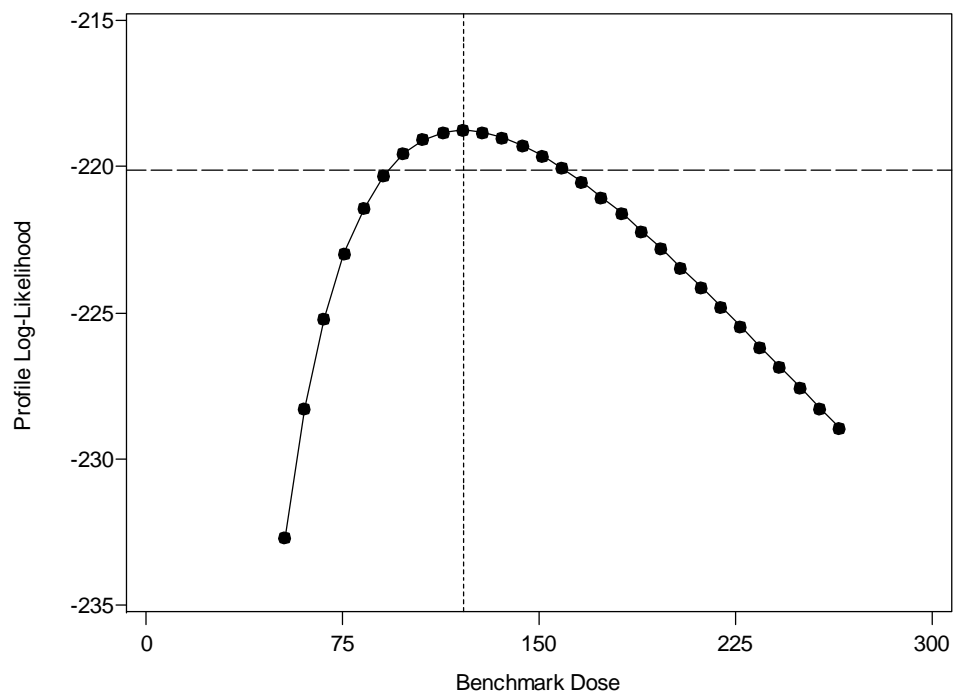
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A4.6. 1-Stage Model, Fixed $t_0 = 19$

A4.6.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-2.147580E+002	5.789571E+000	19	0.000000E+000
BMDs	-2.147580E+002	5.789571E+000	19	0.000000E+000

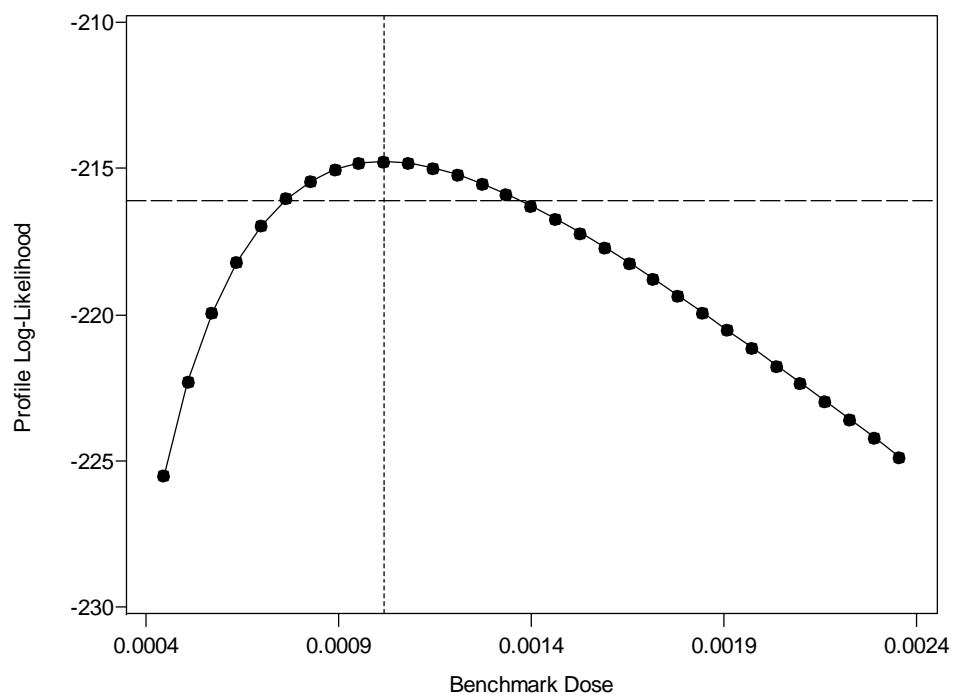
Software	Parameter MLE
	β_1
TOXRISK	2.063400E-012
BMDs	2.063401E-012

A4.6.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

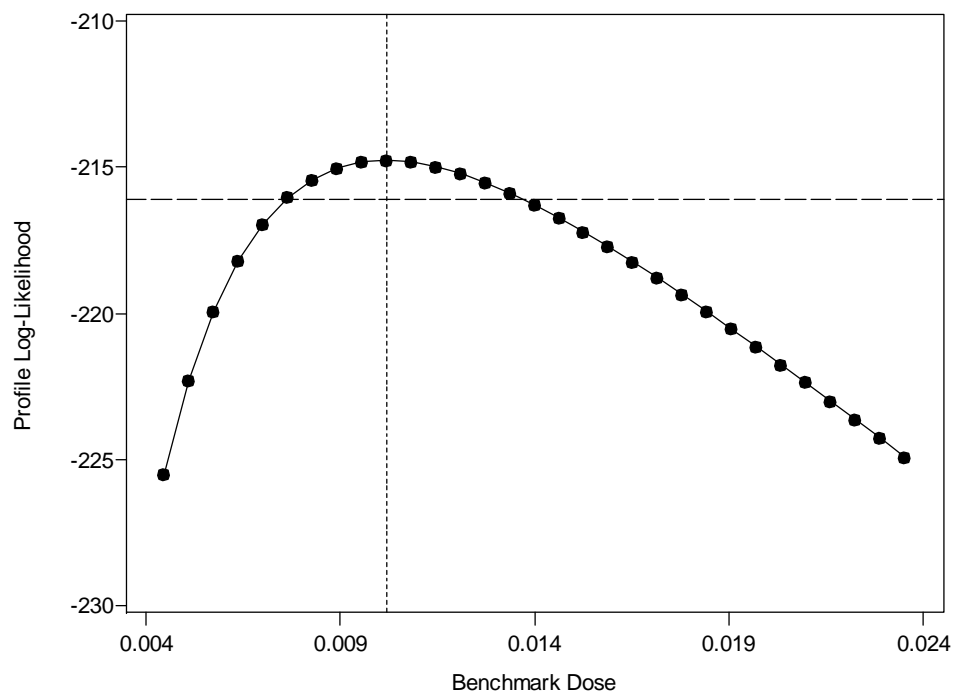
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	7.5689E-004	1.0178E-003	1.3881E-003
	BMDs	7.1545E-004	1.0178E-003	1.4577E-003
1.0E-05	TOXRISK	7.5690E-003	1.0178E-002	1.3772E-002
	BMDs	7.1546E-003	1.0178E-002	1.4577E-002
1.0E-04	TOXRISK	7.5693E-002	1.0178E-001	1.3751E-001
	BMDs	7.1549E-002	1.0178E-001	1.4578E-001
1.0E-03	TOXRISK	7.5727E-001	1.0183E+000	1.3758E+000
	BMDs	7.1584E-001	1.0183E+000	1.4584E+000
1.0E-02	TOXRISK	7.6070E+000	1.0229E+001	1.3821E+001
	BMDs	7.1905E+000	1.0229E+001	1.4650E+001
1.0E-01	TOXRISK	7.9747E+001	1.0723E+002	1.4488E+002
	BMDs	7.5381E+001	1.0723E+002	1.5358E+002

A4.6.3. Plots of Profile Log-Likelihood Functions

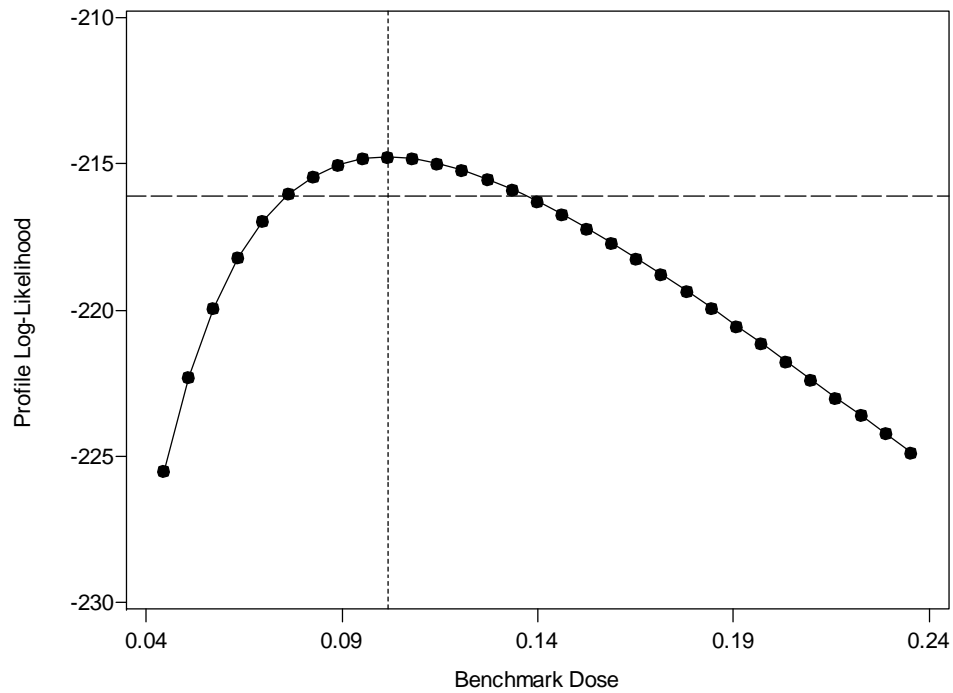
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



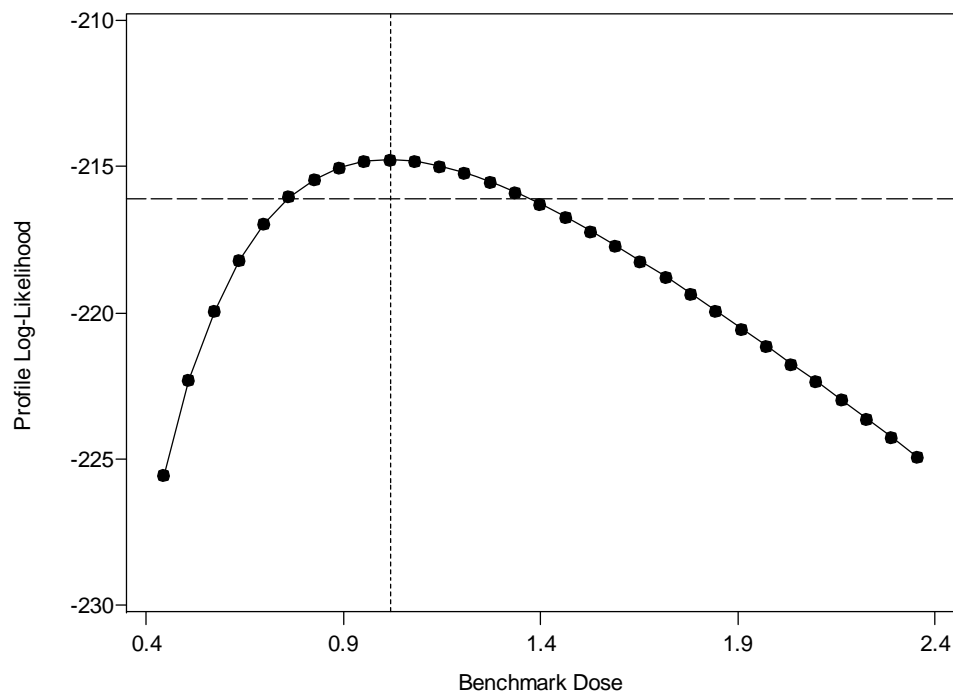
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



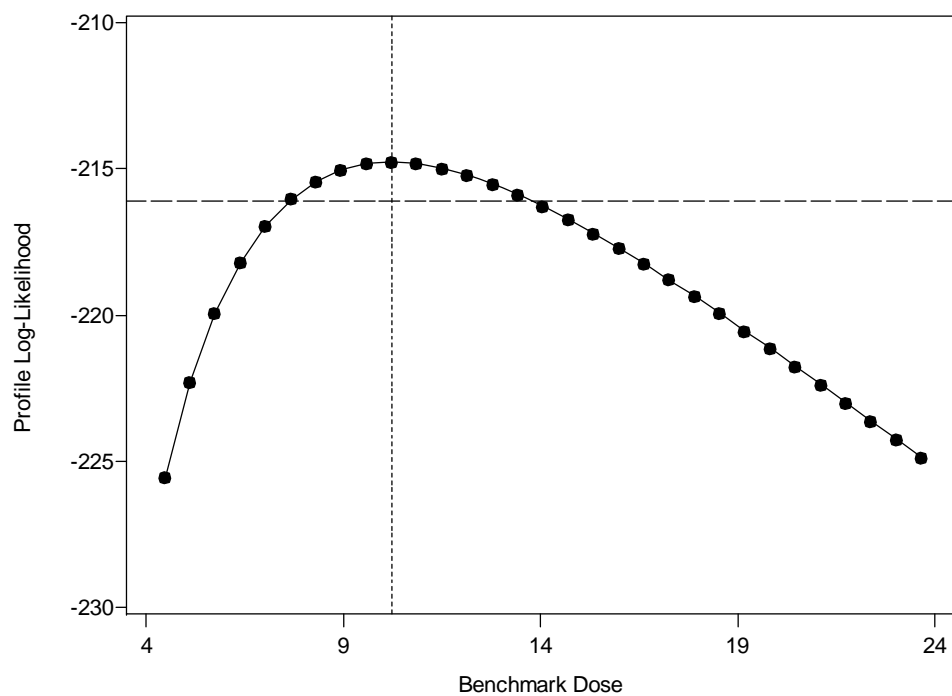
Incidental Extra Risk = 1.0E-04 at 104 Weeks



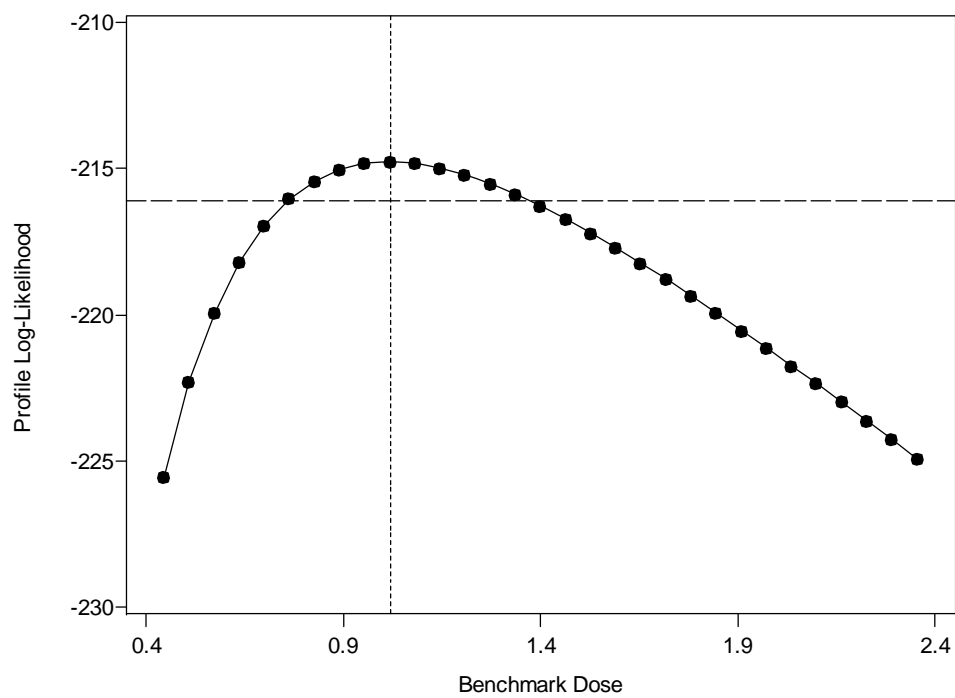
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5. Simulated Dataset 2 (sim11jun07b)

A5.1. 3-Stage Model, Fixed $t_0 = 14$

A5.1.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.877375E+002	7.294400E+000	14	1.761875E-015
BMDS	-4.877375E+002	7.294401E+000	14	1.761871E-015

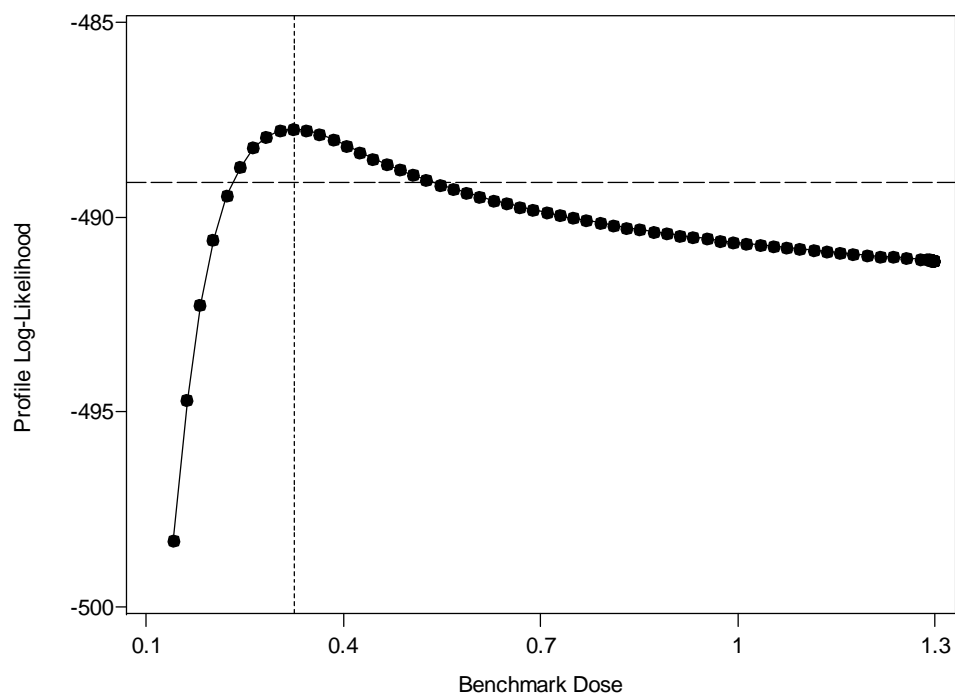
Software	Parameter MLE		
	β_1	β_2	β_3
TOXRISK	5.962044E-018	0.000000E+000	0.000000E+000
BMDS	5.962031E-018	0.000000E+000	0.000000E+000

A5.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

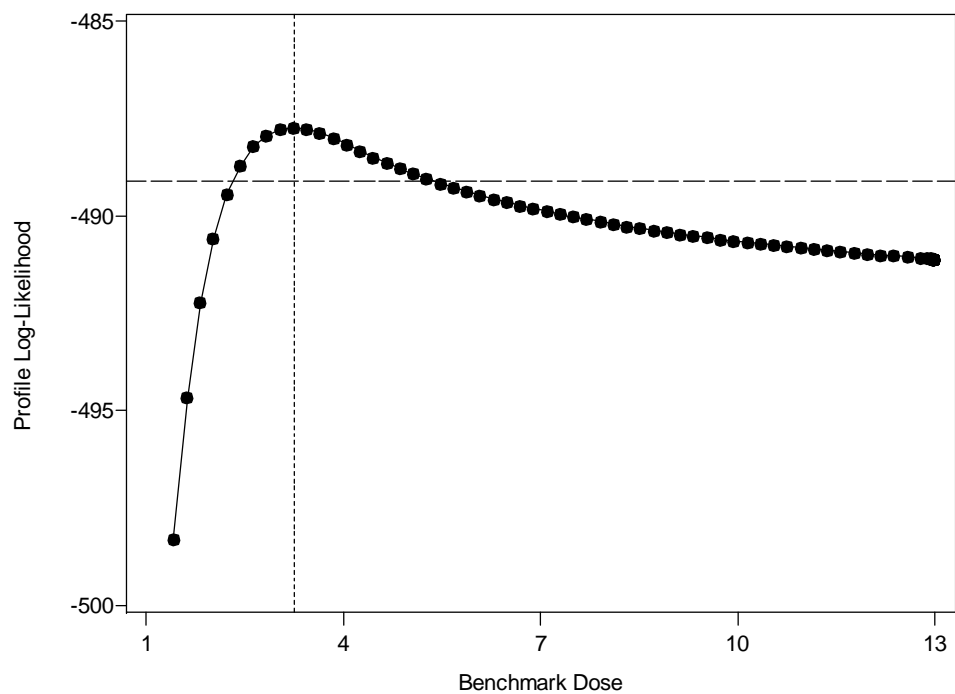
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	2.3177E-001	3.2476E-001	5.3564E-001
	BMDS	2.1871E-001	3.2476E-001	6.5077E-001
1.0E-05	TOXRISK	2.3178E+000	3.2476E+000	5.3492E+000
	BMDS	2.1871E+000	3.2476E+000	6.5077E+000
1.0E-04	TOXRISK	2.3179E+001	3.2477E+001	5.3512E+001
	BMDS	2.1872E+001	3.2477E+001	6.5077E+001
1.0E-03	TOXRISK	2.3189E+002	3.2492E+002	5.3528E+002
	BMDS	2.1883E+002	3.2492E+002	6.5078E+002
1.0E-02	TOXRISK	2.3294E+003	3.2639E+003	5.3670E+003
	BMDS	2.1981E+003	3.2639E+003	6.5088E+003
1.0E-01	TOXRISK	2.4420E+004	3.4216E+004	5.5252E+004
	BMDS	2.3043E+004	3.4216E+004	6.5482E+004

A5.1.3. Plots of Profile Log-Likelihood Functions

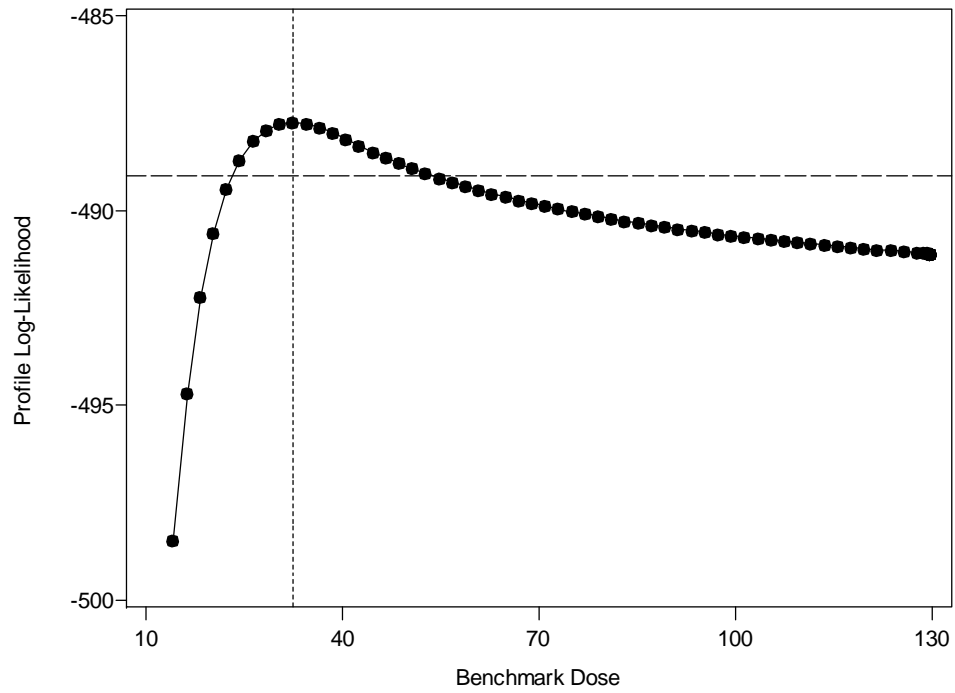
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



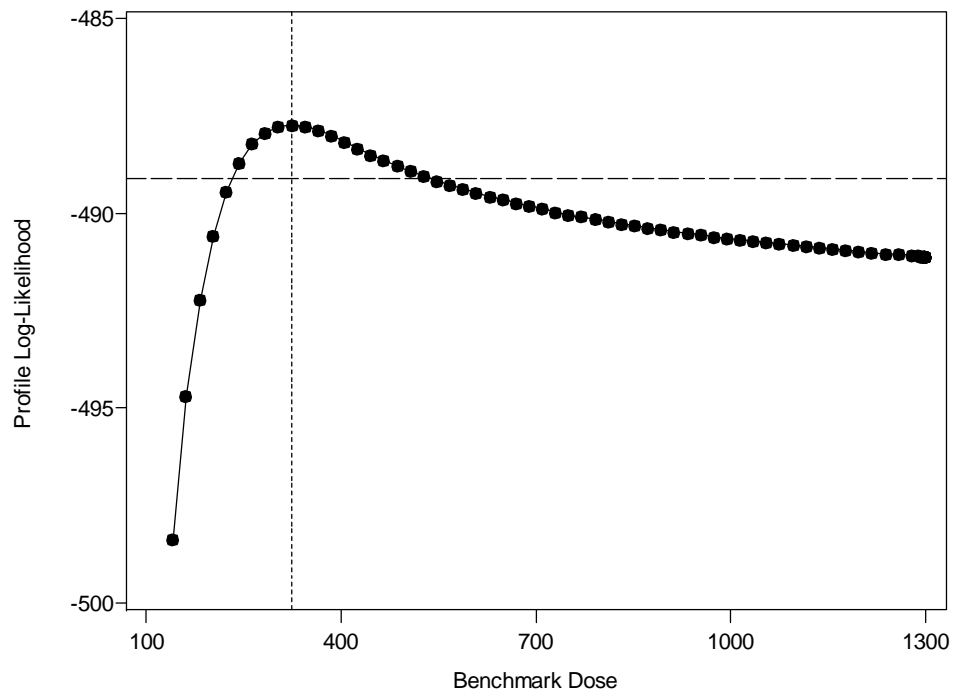
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



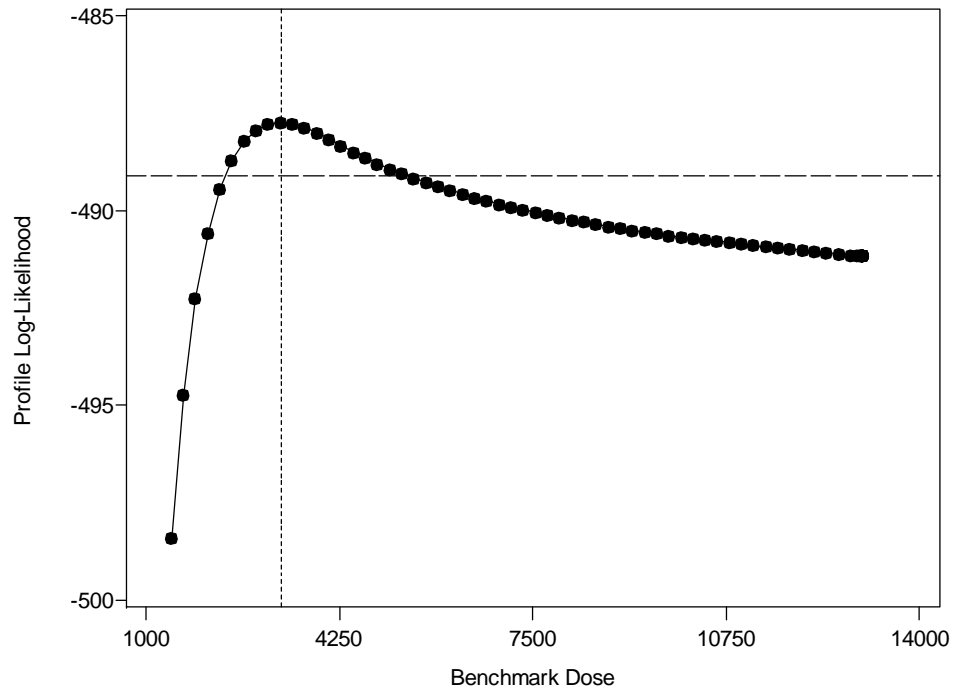
Incidental Extra Risk = 1.0E-04 at 104 Weeks



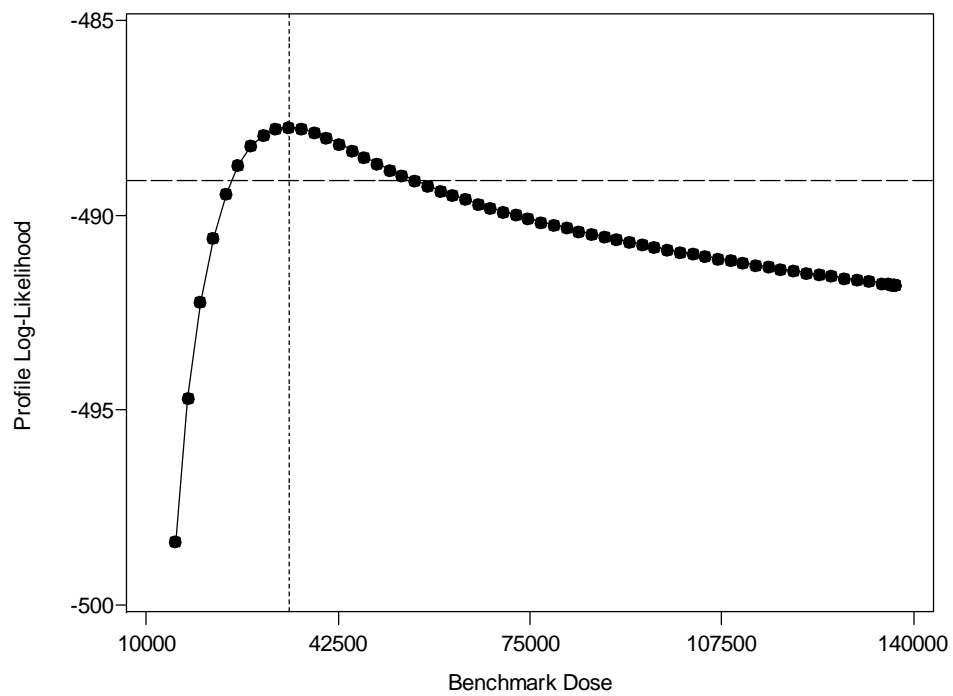
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5.2. 3-Stage Model, Fixed $t_0 = 30$

A5.2.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.892927E+002	4.148900E+000	30	3.995559E-009
BMDS	-4.892927E+002	4.148900E+000	30	3.995559E-009

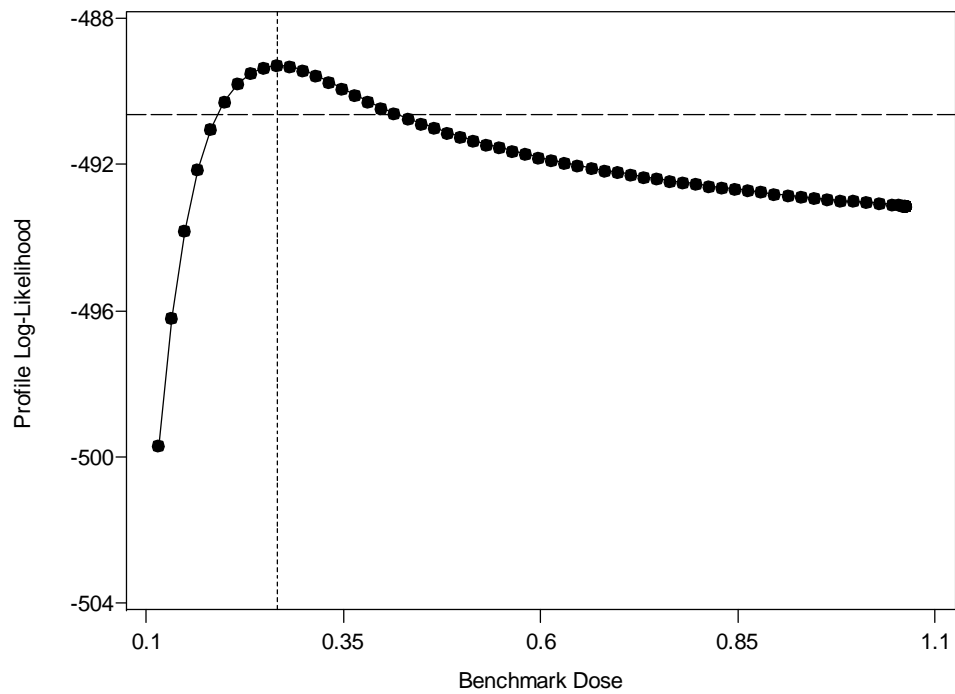
Software	Parameter MLE		
	β_1	β_2	β_3
TOXRISK	1.609952E-011	0.000000E+000	0.000000E+000
BMDS	1.609952E-011	0.000000E+000	0.000000E+000

A5.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

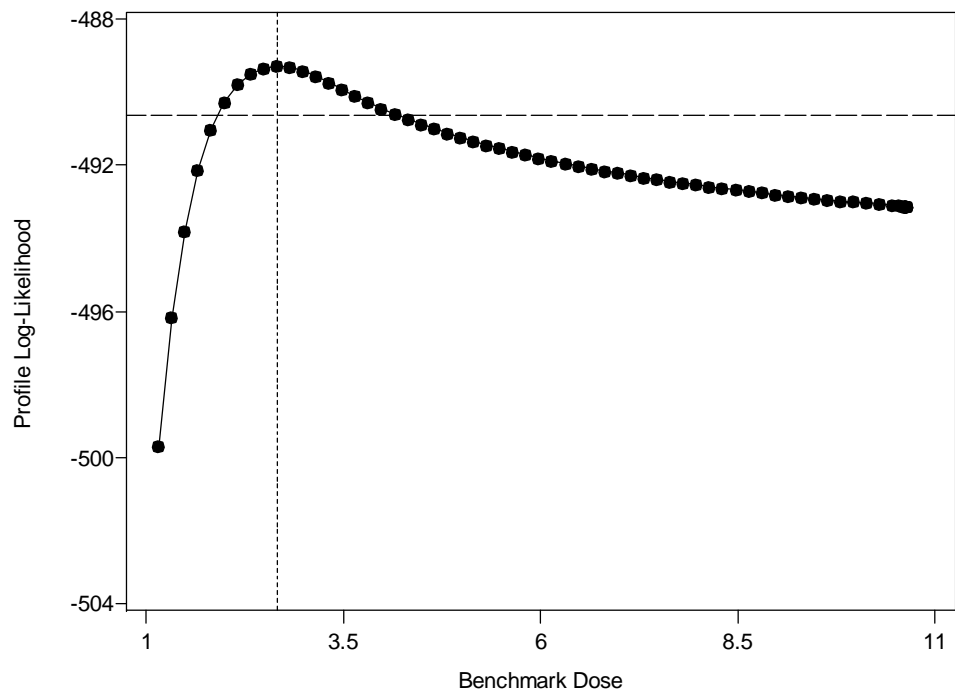
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	1.9019E-001	2.6590E-001	4.2080E-001
	BMDS	1.7941E-001	2.6590E-001	4.9539E-001
1.0E-05	TOXRISK	1.9019E+000	2.6590E+000	4.2080E+000
	BMDS	1.7943E+000	2.6590E+000	4.9539E+000
1.0E-04	TOXRISK	1.9020E+001	2.6591E+001	4.2057E+001
	BMDS	1.7942E+001	2.6591E+001	4.9540E+001
1.0E-03	TOXRISK	1.9029E+002	2.6603E+002	4.2070E+002
	BMDS	1.7950E+002	2.6603E+002	4.9550E+002
1.0E-02	TOXRISK	1.9115E+003	2.6724E+003	4.2213E+003
	BMDS	1.8032E+003	2.6724E+003	4.9646E+003
1.0E-01	TOXRISK	2.0039E+004	2.8015E+004	4.3769E+004
	BMDS	1.8903E+004	2.8015E+004	5.0759E+004

A5.2.3. Plots of Profile Log-Likelihood Functions

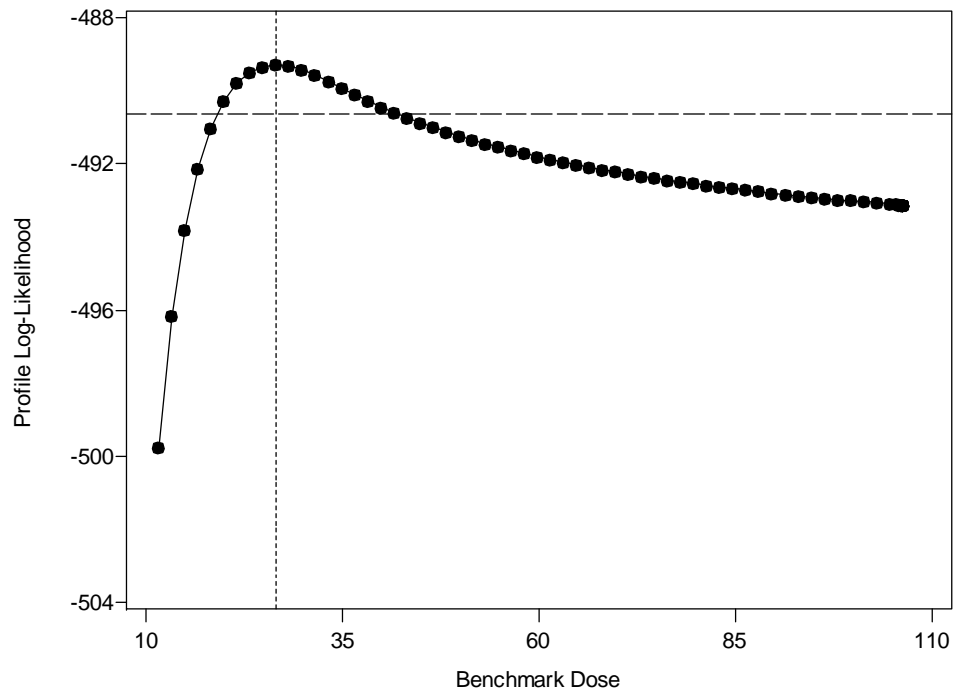
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



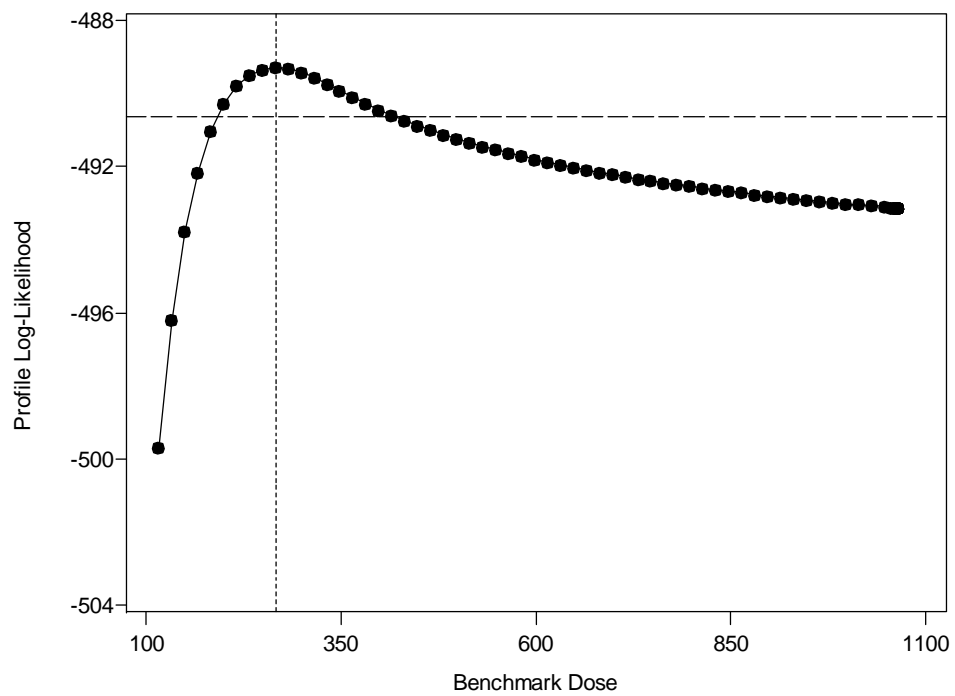
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



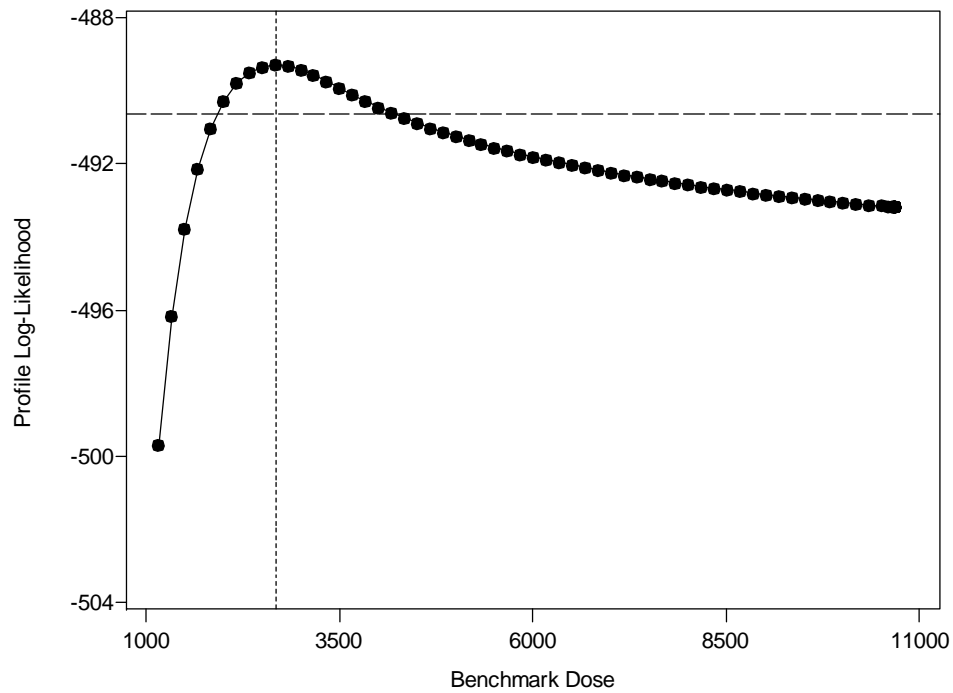
Incidental Extra Risk = 1.0E-04 at 104 Weeks



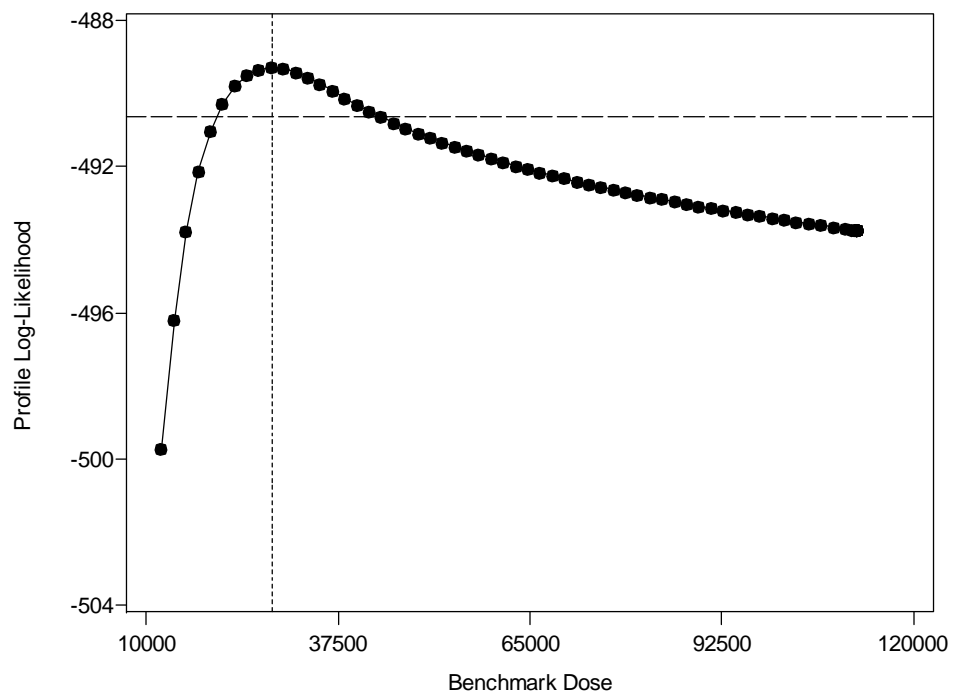
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5.3. 2-Stage Model, Fixed $t_0 = 14$

A5.3.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.877375E+002	7.294400E+000	14	1.761875E-015
BMDS	-4.877375E+002	7.294401E+000	14	1.761872E-015

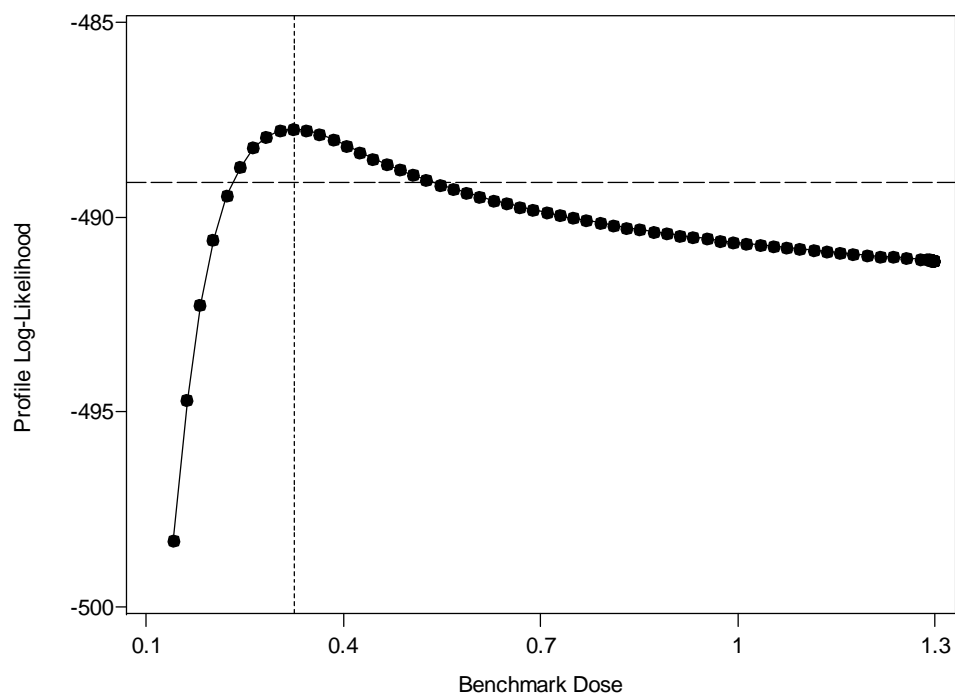
Software	Parameter MLE	
	β_1	β_2
TOXRISK	5.962044E-018	0.000000E+000
BMDS	5.962035E-018	0.000000E+000

A5.3.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

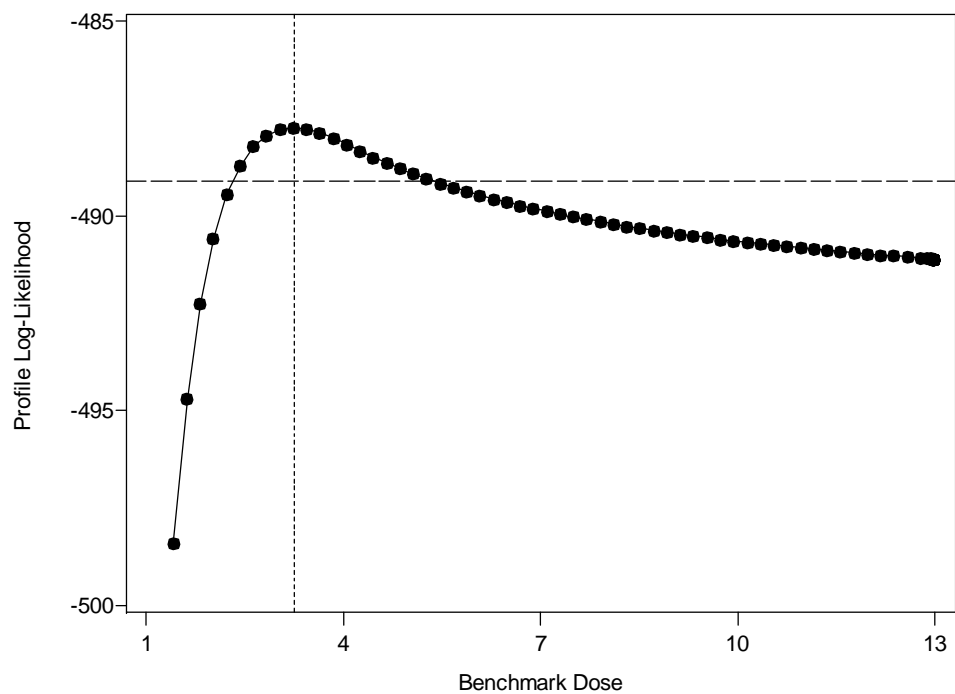
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	2.3177E-001	3.2476E-001	5.3564E-001
	BMDS	2.1871E-001	3.2476E-001	6.5077E-001
1.0E-05	TOXRISK	2.3178E+000	3.2476E+000	5.3492E+000
	BMDS	2.1871E+000	3.2476E+000	6.5077E+000
1.0E-04	TOXRISK	2.3179E+001	3.2477E+001	5.3512E+001
	BMDS	2.1872E+001	3.2477E+001	6.5077E+001
1.0E-03	TOXRISK	2.3189E+002	3.2492E+002	5.3528E+002
	BMDS	2.1882E+002	3.2492E+002	6.5077E+002
1.0E-02	TOXRISK	2.3294E+003	3.2639E+003	5.3670E+003
	BMDS	2.1982E+003	3.2639E+003	6.5088E+003
1.0E-01	TOXRISK	2.4420E+004	3.4216E+004	5.5252E+004
	BMDS	2.3045E+004	3.4216E+004	6.5482E+004

A5.3.3. Plots of Profile Log-Likelihood Functions

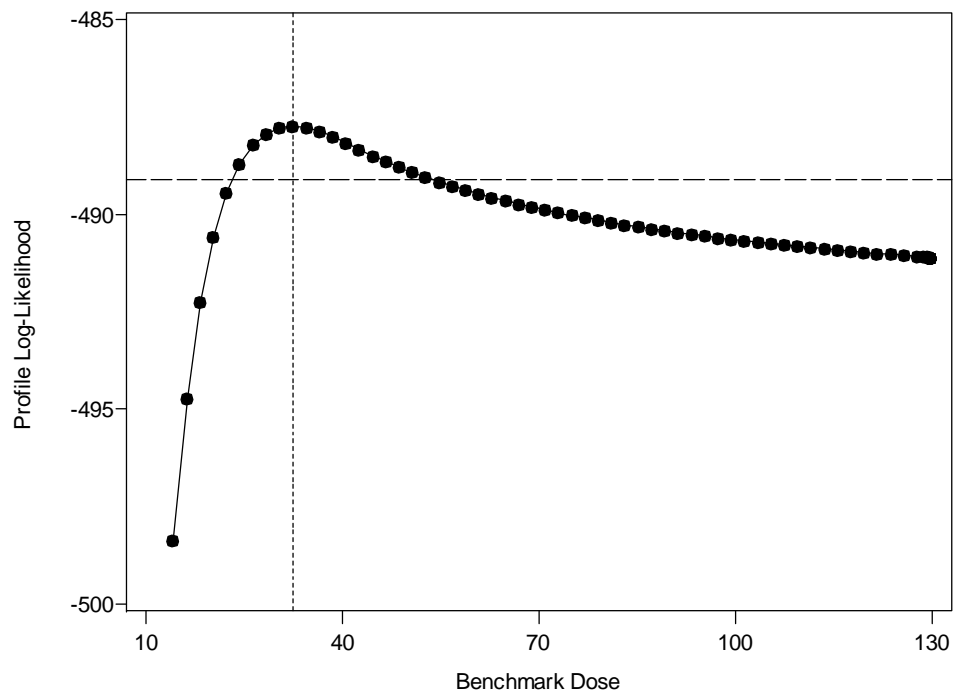
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



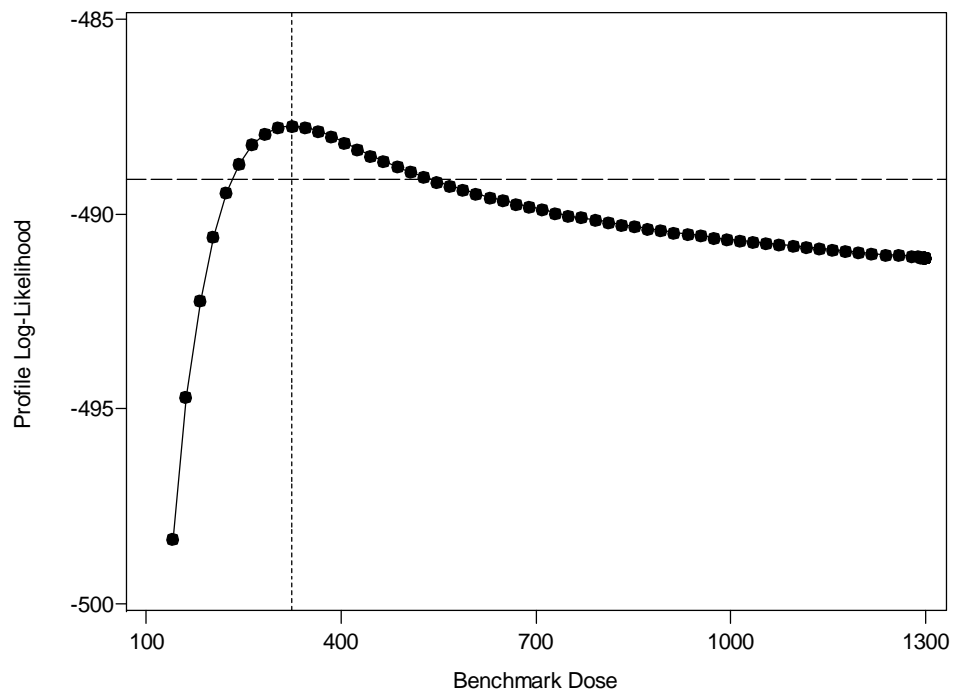
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



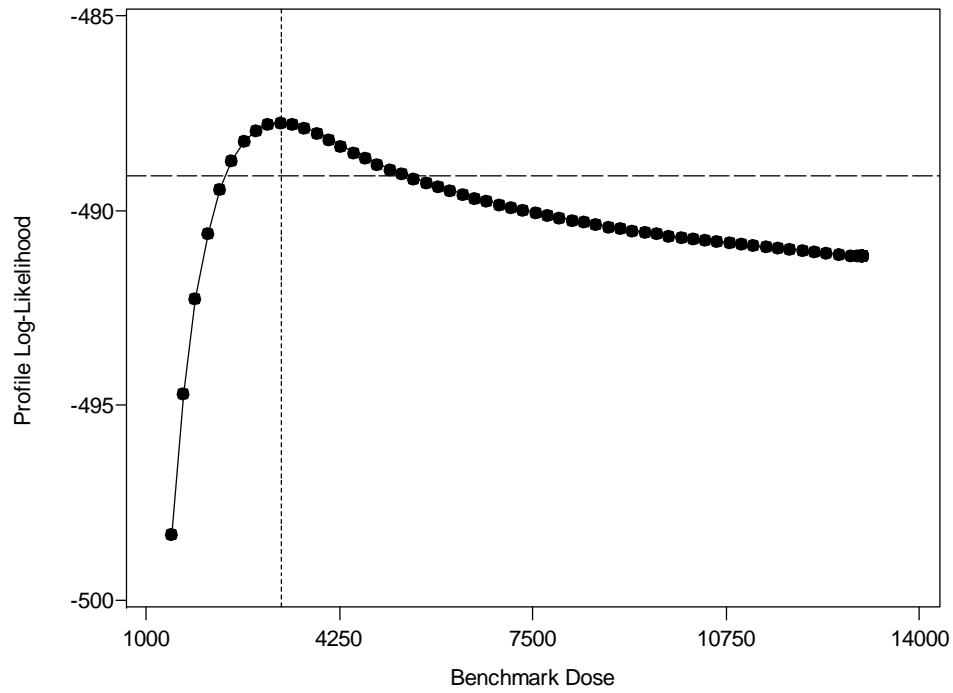
Incidental Extra Risk = 1.0E-04 at 104 Weeks



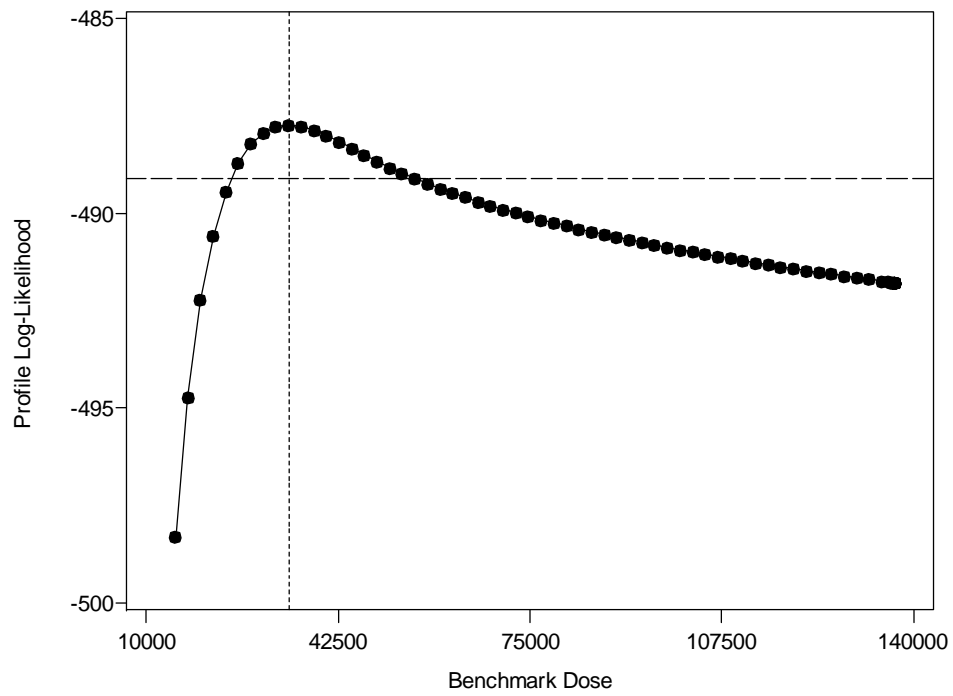
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5.4. 2-Stage Model, Fixed $t_0 = 30$

A5.4.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.892927E+002	4.148900E+000	30	3.995559E-009
BMDS	-4.892927E+002	4.148900E+000	30	3.995560E-009

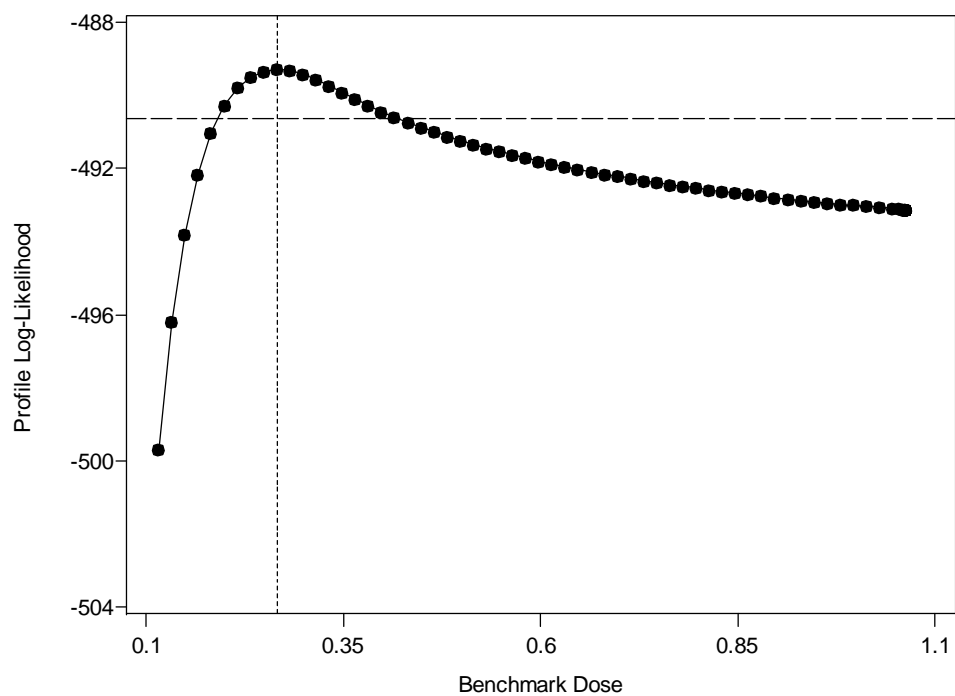
Software	Parameter MLE	
	β_1	β_2
TOXRISK	1.609952E-011	0.000000E+000
BMDS	1.609952E-011	0.000000E+00

A5.4.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

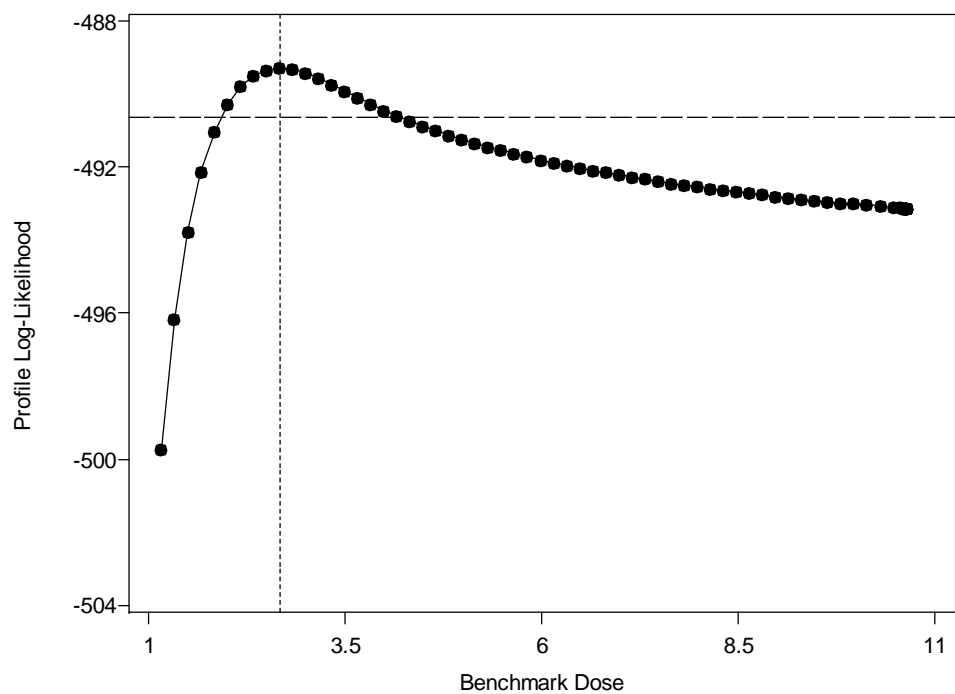
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	1.9019E-001	2.6590E-001	4.2080E-001
	BMDS	1.7941E-001	2.6590E-001	4.9539E-001
1.0E-05	TOXRISK	1.9019E+000	2.6590E+000	4.2080E+000
	BMDS	1.7941E+000	2.6590E+000	4.9539E+000
1.0E-04	TOXRISK	1.9020E+001	2.6591E+001	4.2057E+001
	BMDS	1.7942E+001	2.6591E+001	4.9540E+001
1.0E-03	TOXRISK	1.9029E+002	2.6603E+002	4.2070E+002
	BMDS	1.7950E+002	2.6603E+002	4.9550E+002
1.0E-02	TOXRISK	1.9115E+003	2.6724E+003	4.2213E+003
	BMDS	1.8031E+003	2.6724E+003	4.9646E+003
1.0E-01	TOXRISK	2.0039E+004	2.8015E+004	4.3769E+004
	BMDS	1.8903E+004	2.8015E+004	5.0759E+004

A5.4.3. Plots of Profile Log-Likelihood Functions

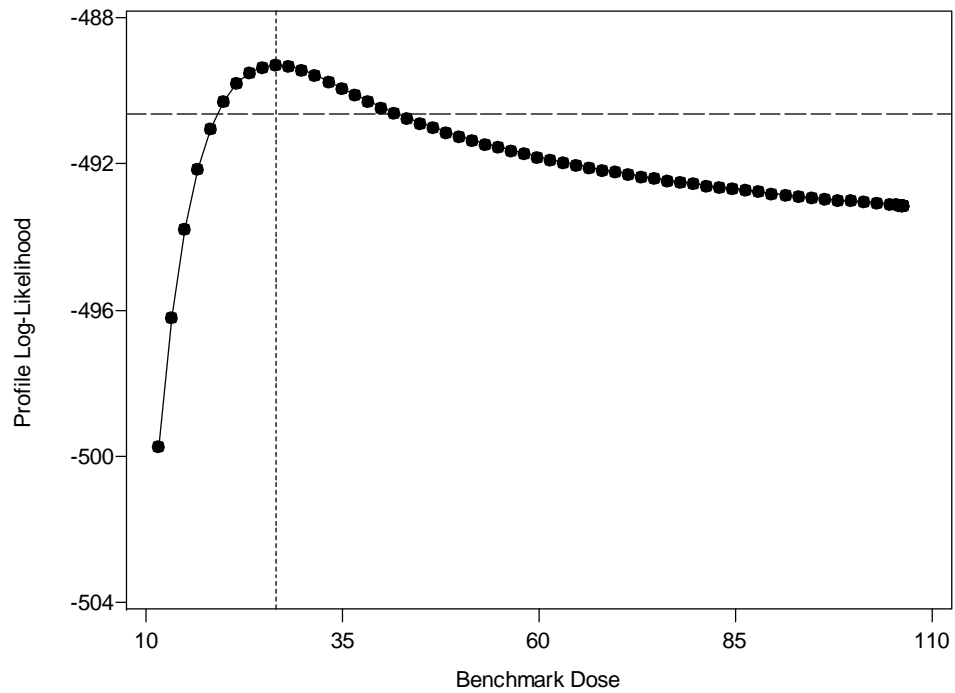
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



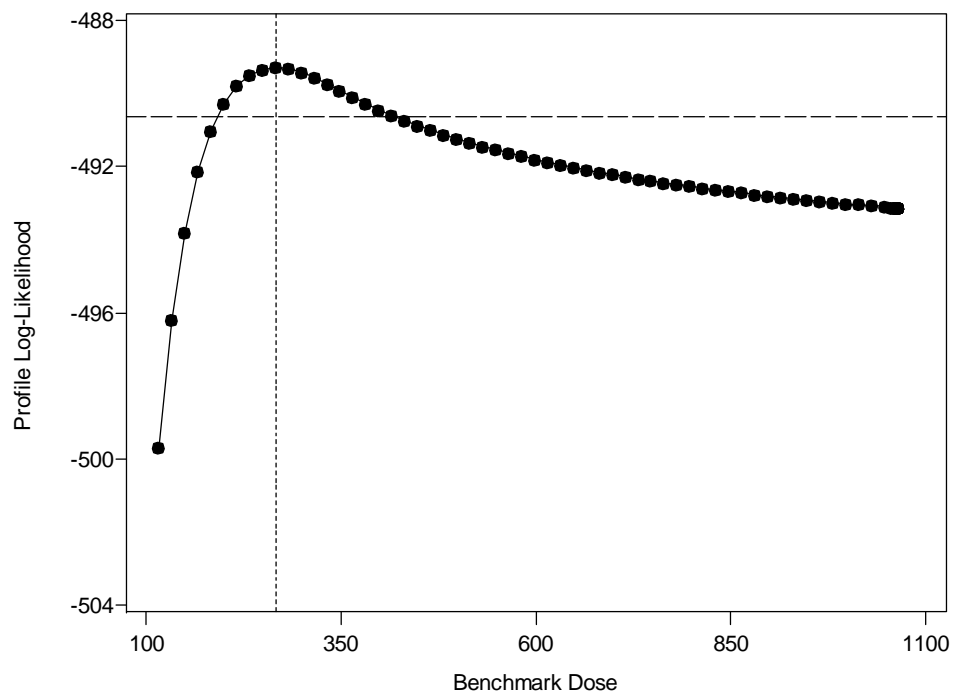
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



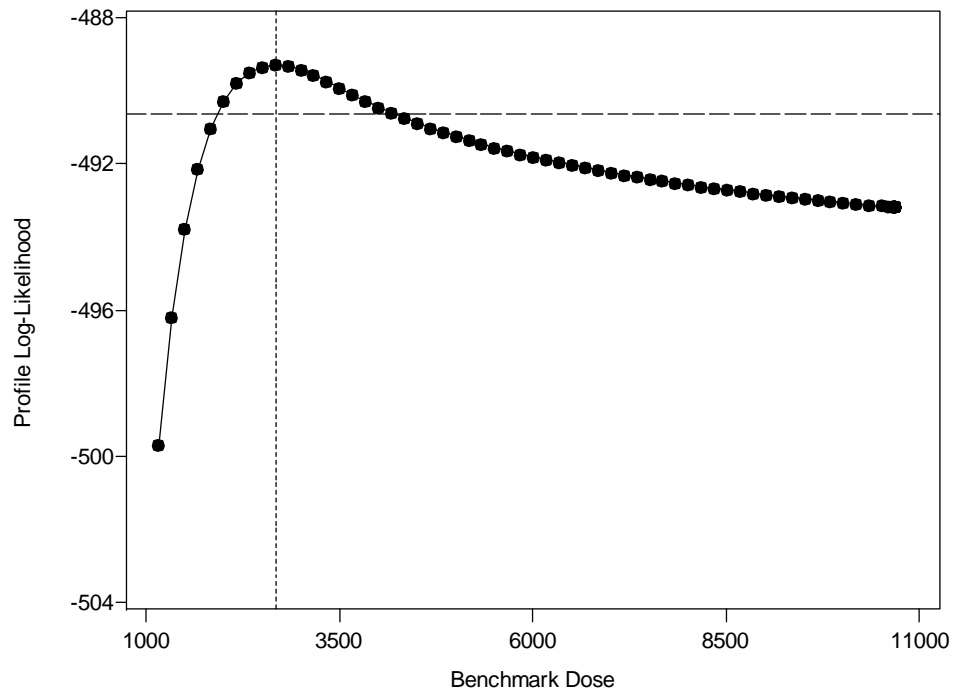
Incidental Extra Risk = 1.0E-04 at 104 Weeks



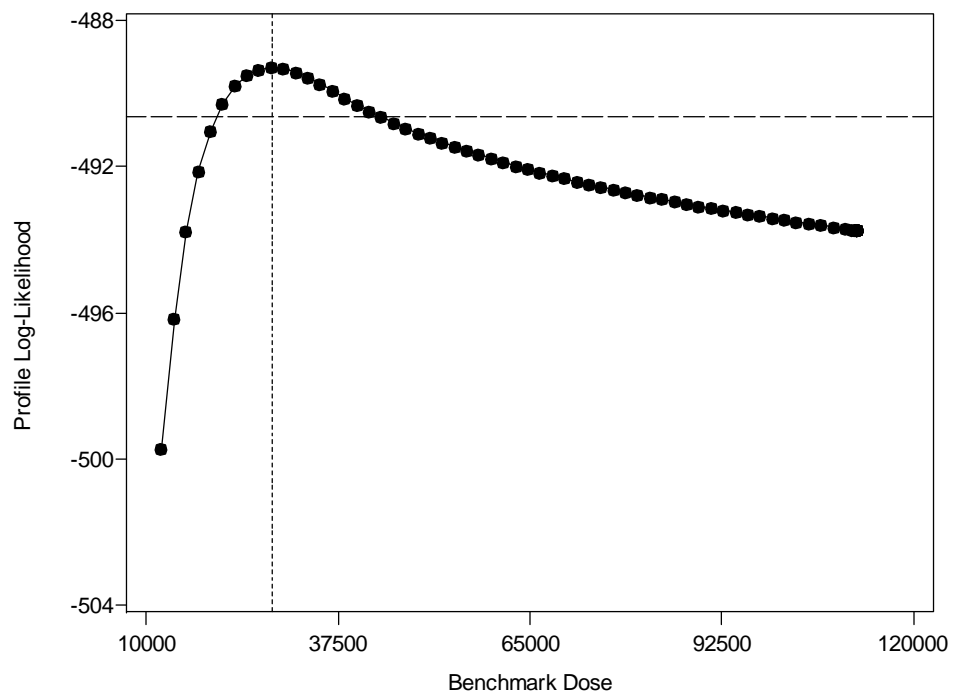
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5.5. 1-Stage Model, Fixed $t_0 = 14$

A5.5.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.877375E+002	7.294400E+000	14	1.761875E-015
BMDS	-4.877375E+002	7.294400E+000	14	1.761875E-015

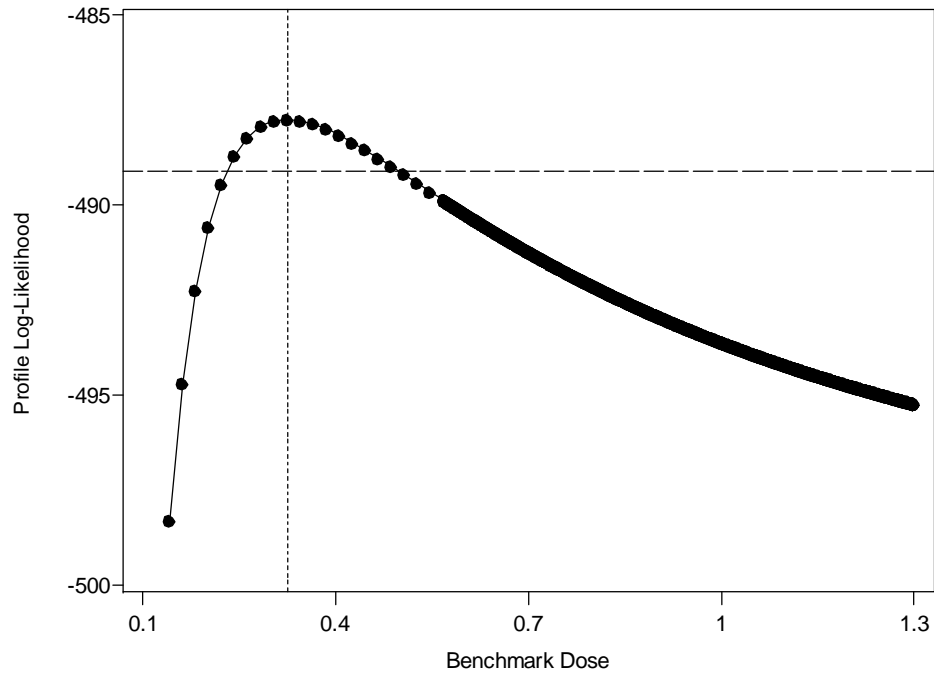
Software	Parameter MLE
	β_1
TOXRISK	5.962044E-018
BMDS	5.962045E-018

A5.5.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

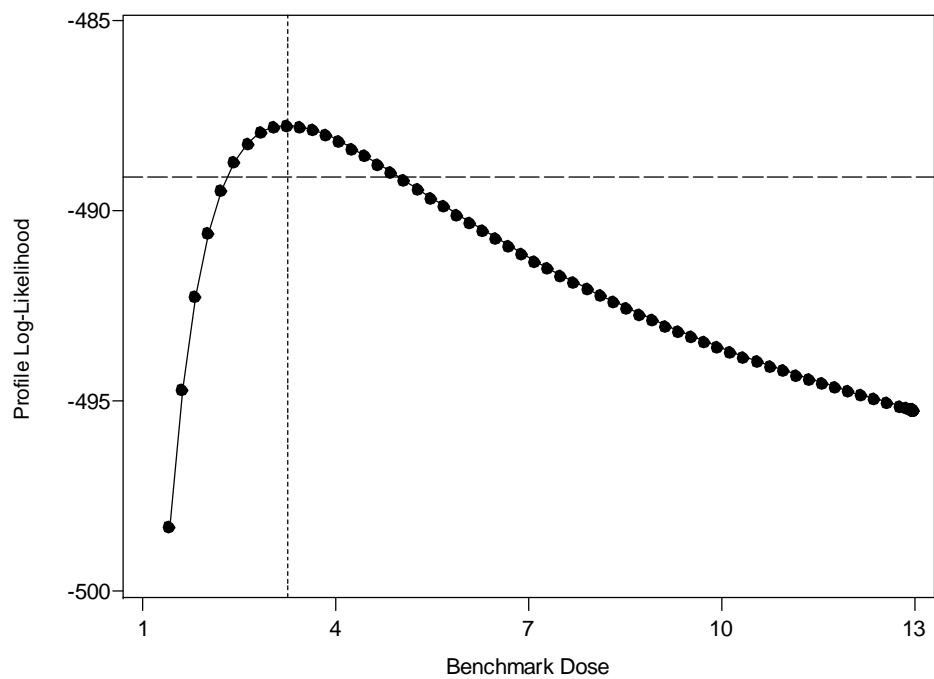
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	2.3177E-001	3.2476E-001	4.9977E-001
	BMDS	2.1871E-001	3.2476E-001	5.6452E-001
1.0E-05	TOXRISK	2.3178E+000	3.2476E+000	4.9845E+000
	BMDS	2.1872E+000	3.2476E+000	5.4992E+000
1.0E-04	TOXRISK	2.3179E+001	3.2477E+001	4.9817E+001
	BMDS	2.1872E+001	3.2477E+001	5.4995E+001
1.0E-03	TOXRISK	2.3189E+002	3.2492E+002	4.9839E+002
	BMDS	2.1883E+002	3.2492E+002	5.5019E+002
1.0E-02	TOXRISK	2.3294E+003	3.2639E+003	5.0065E+003
	BMDS	2.1981E+003	3.2639E+003	5.5269E+003
1.0E-01	TOXRISK	2.4420E+004	3.4216E+004	5.2485E+004
	BMDS	2.3043E+004	3.4216E+004	5.7940E+004

A5.5.3. Plots of Profile Log-Likelihood Functions

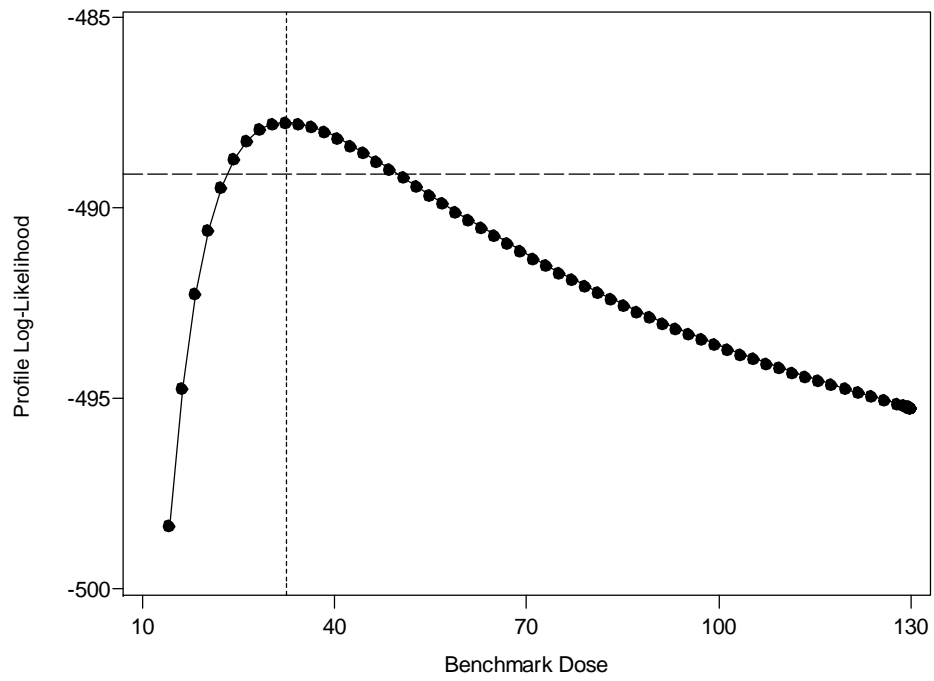
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



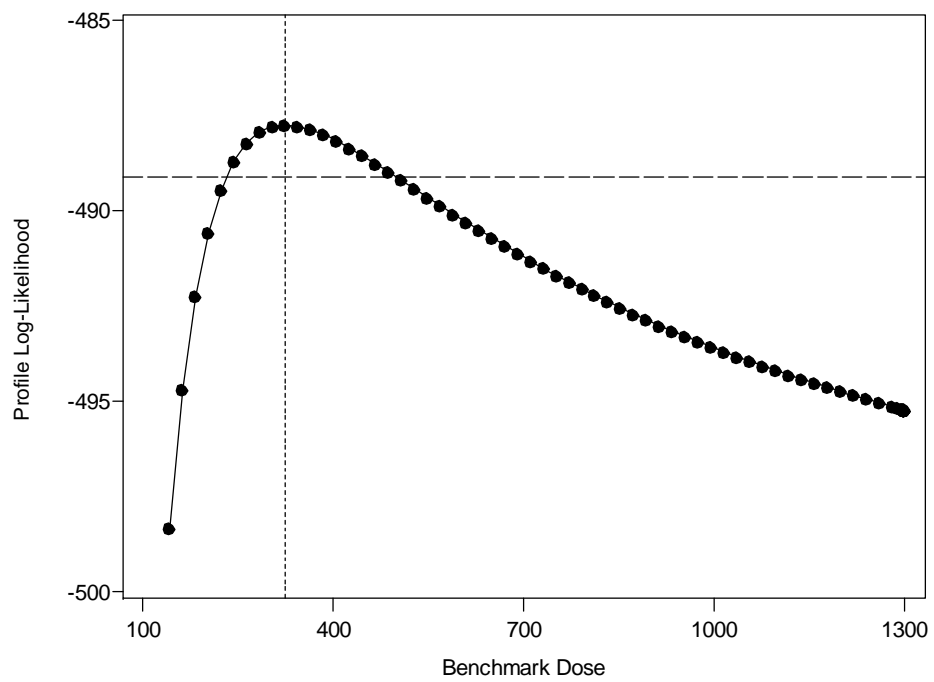
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



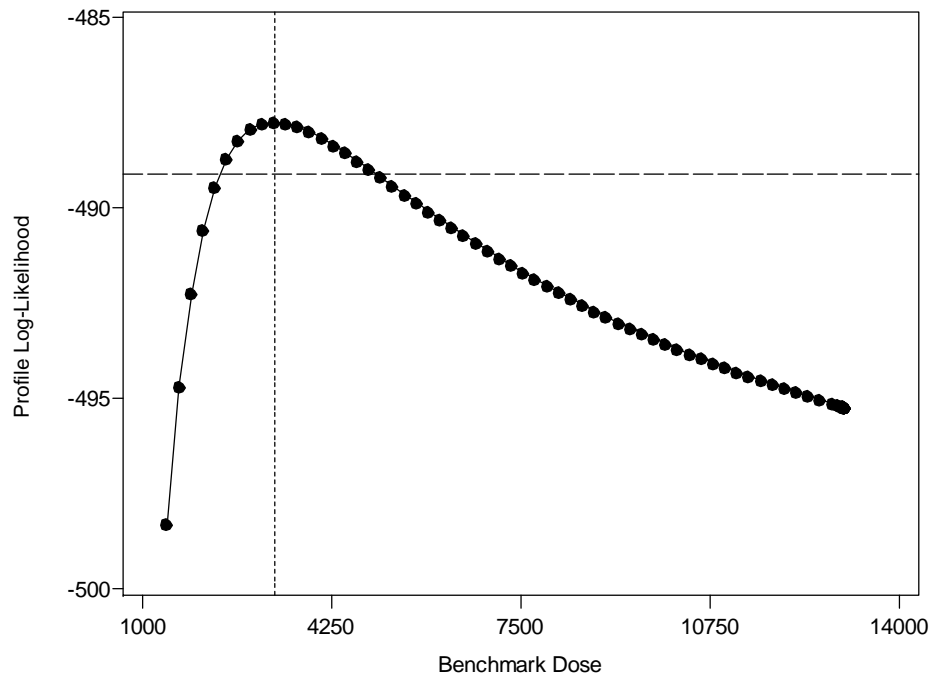
Incidental Extra Risk = 1.0E-04 at 104 Weeks



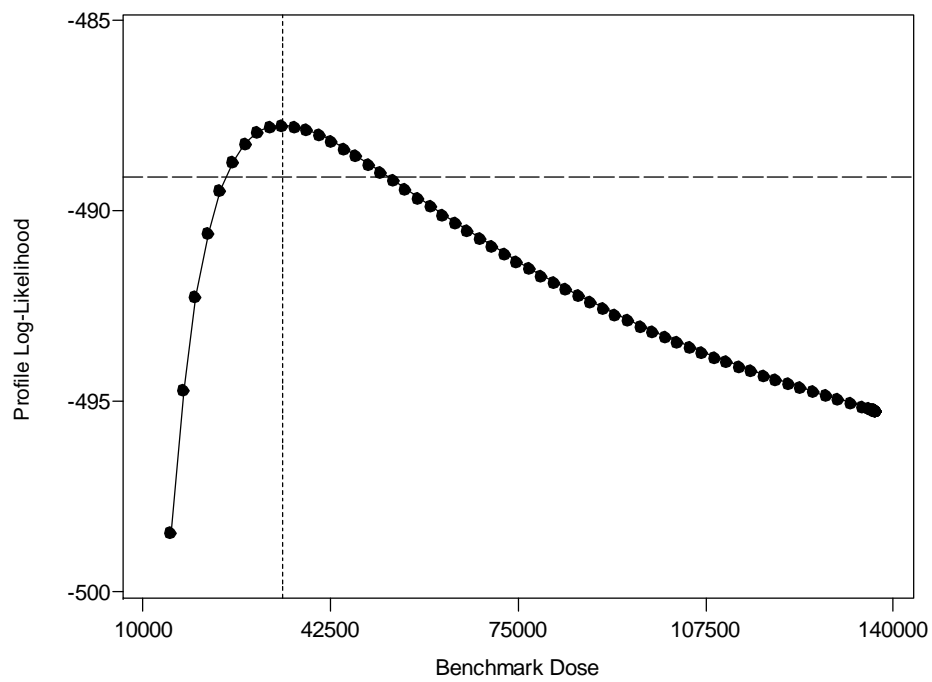
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



A5.6. 1-Stage Model, Fixed $t_0 = 30$

A5.6.1. Model Parameters

Software	Log-Likelihood	Parameter MLE (Except t_0 Fixed)		
		c	t_0	β_0
TOXRISK	-4.892927E+002	4.148900E+000	30	3.995559E-009
BMDS	-4.892927E+002	4.148900E+000	30	3.995560E-009

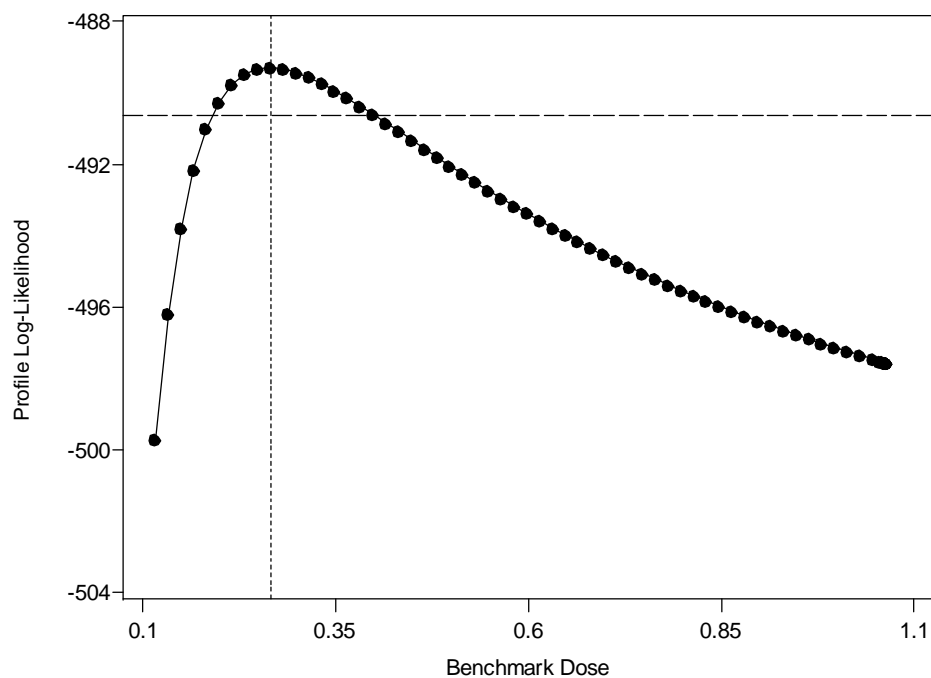
Software	Parameter MLE
	β_1
TOXRISK	1.609952E-011
BMDS	1.609952E-011

A5.6.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

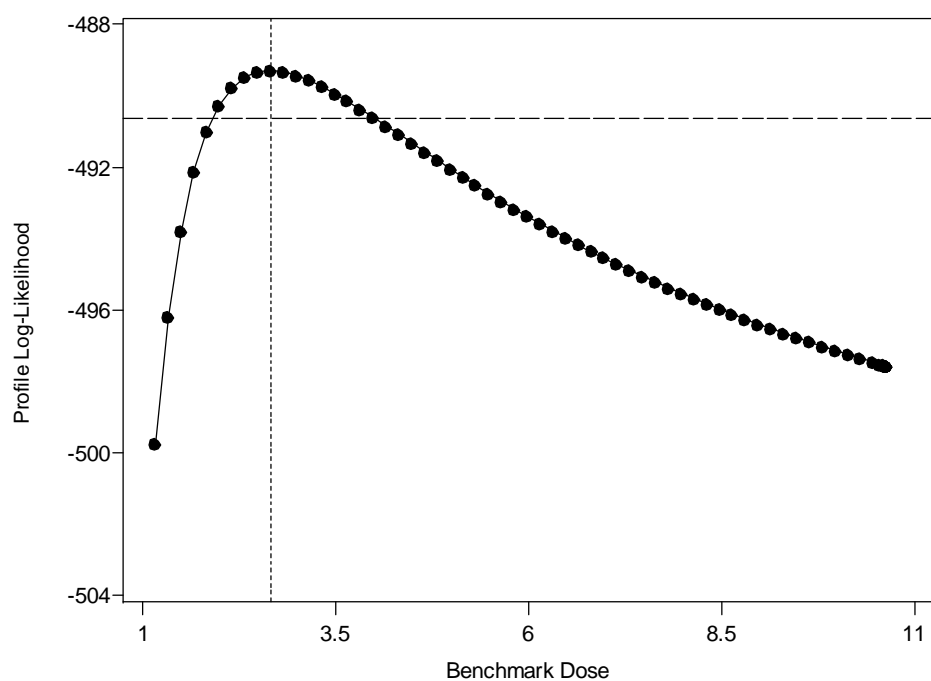
Incidental Extra Risk at 104 Weeks	Software	BMD		
		Lower 95% Bound	MLE	Upper 95% Bound
1.0E-06	TOXRISK	1.9019E-001	2.6590E-001	4.0499E-001
	BMDS	1.7941E-001	2.6590E-001	4.4097E-001
1.0E-05	TOXRISK	1.9019E+000	2.6590E+000	4.0179E+000
	BMDS	1.7941E+000	2.6590E+000	4.4097E+000
1.0E-04	TOXRISK	1.9020E+001	2.6591E+001	4.0178E+001
	BMDS	1.7942E+001	2.6591E+001	4.4099E+001
1.0E-03	TOXRISK	1.9029E+002	2.6603E+002	4.0195E+002
	BMDS	1.7950E+002	2.6603E+002	4.4118E+002
1.0E-02	TOXRISK	1.9115E+003	2.6724E+003	4.0377E+003
	BMDS	1.8031E+003	2.6724E+003	4.4318E+003
1.0E-01	TOXRISK	2.0039E+004	2.8015E+004	4.2329E+004
	BMDS	1.8903E+004	2.8015E+004	4.6460E+004

A5.6.3. Plots of Profile Log-Likelihood Functions

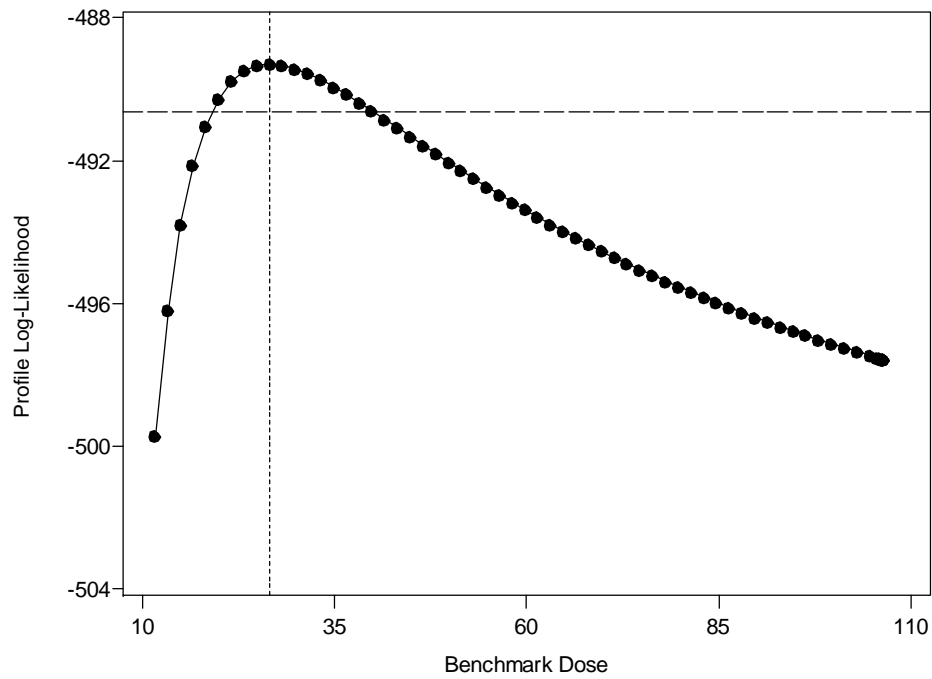
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



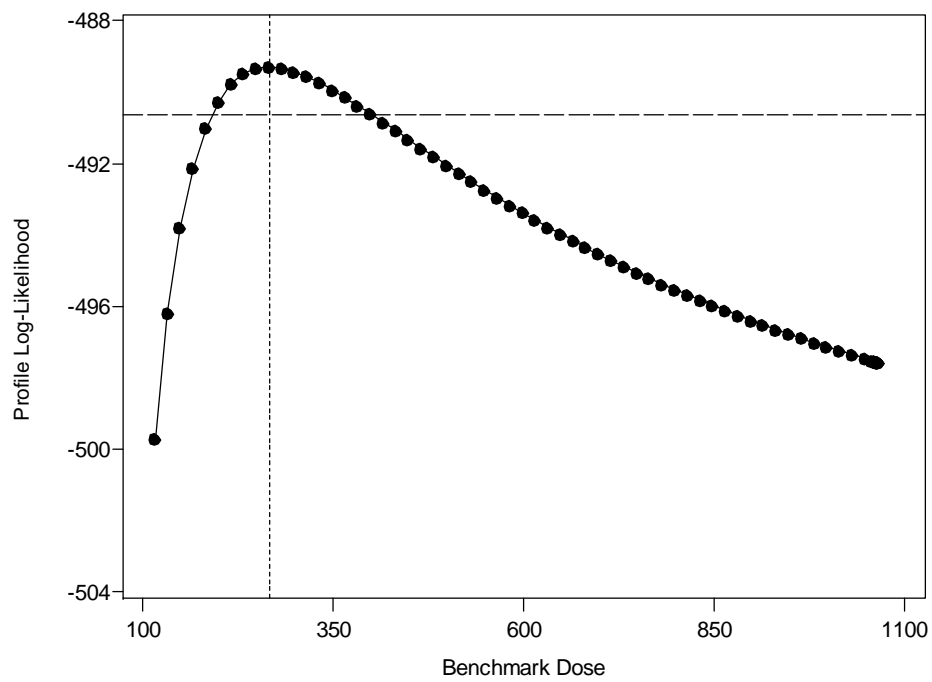
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



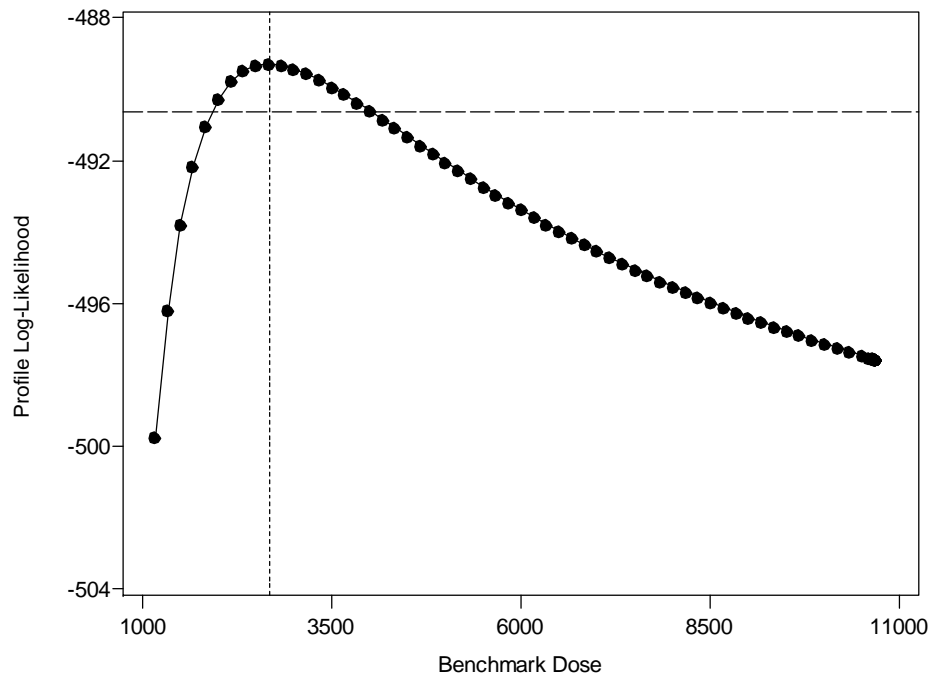
Incidental Extra Risk = $1.0\text{E-}04$ at 104 Weeks



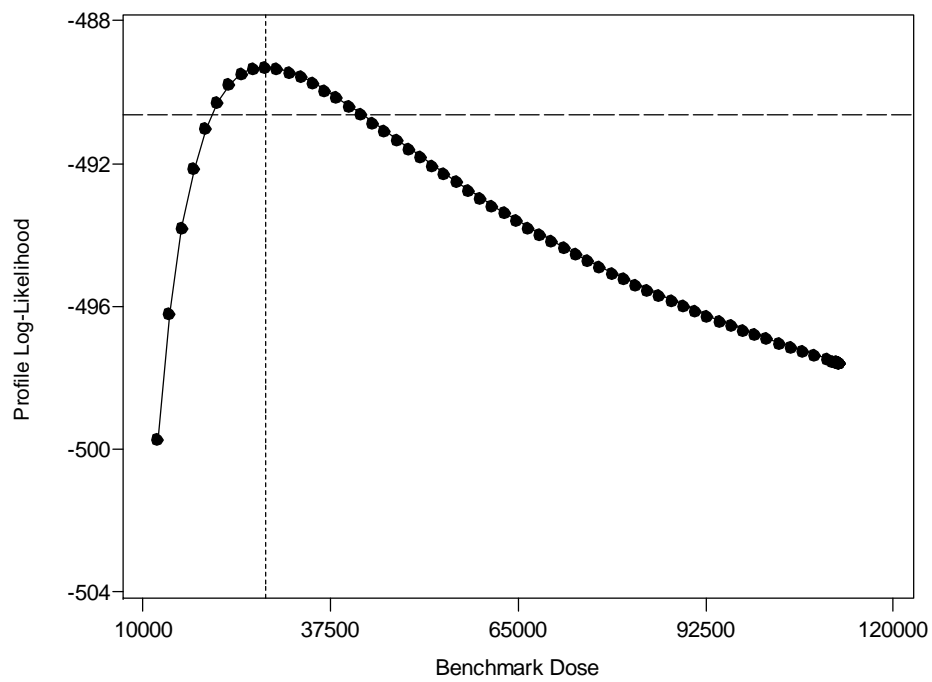
Incidental Extra Risk = $1.0\text{E-}03$ at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



Appendix B

Detailed Listing from Fitting Multistage Weibull Models to Test Datasets Using BMDS (Parameter t_0 Estimated)

B1. Simulated Dataset 1 (sim11jun07a)

B1.1. 3-Stage Model

B1.1.1. Model Parameters

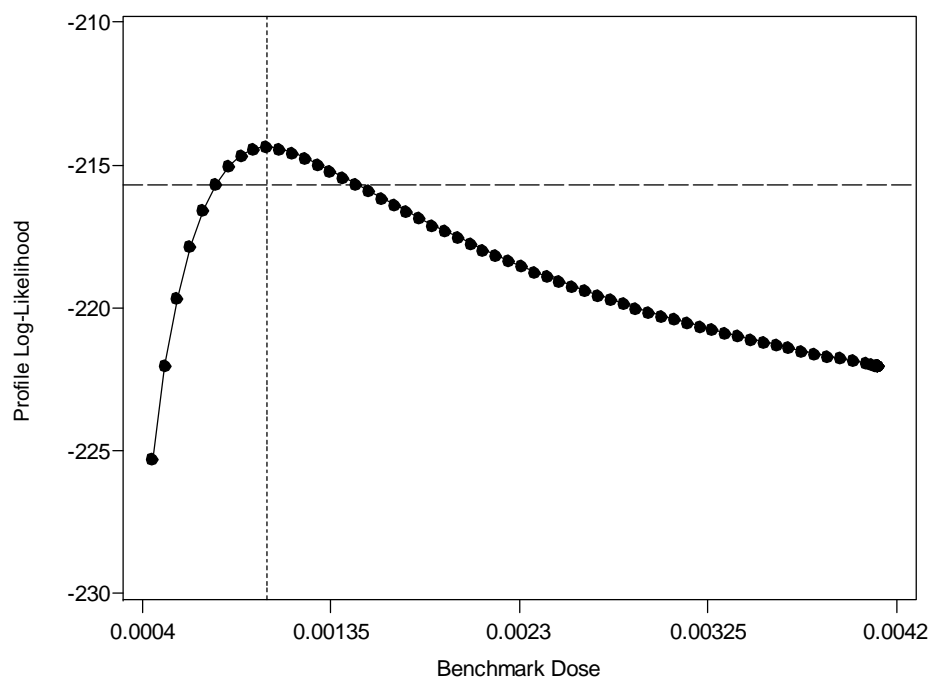
Parameters	MLE (Log-Likelihood = -2.143563E+002)	Simulation Model
c	6.223897E+000	4.86
t_0	1.626028E+001	23
β_0	0.000000E+000	1.03E-011
β_1	2.719038E-013	1.54E-010
β_2	0.000000E+000	0
β_3	0.000000E+000	0

B1.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

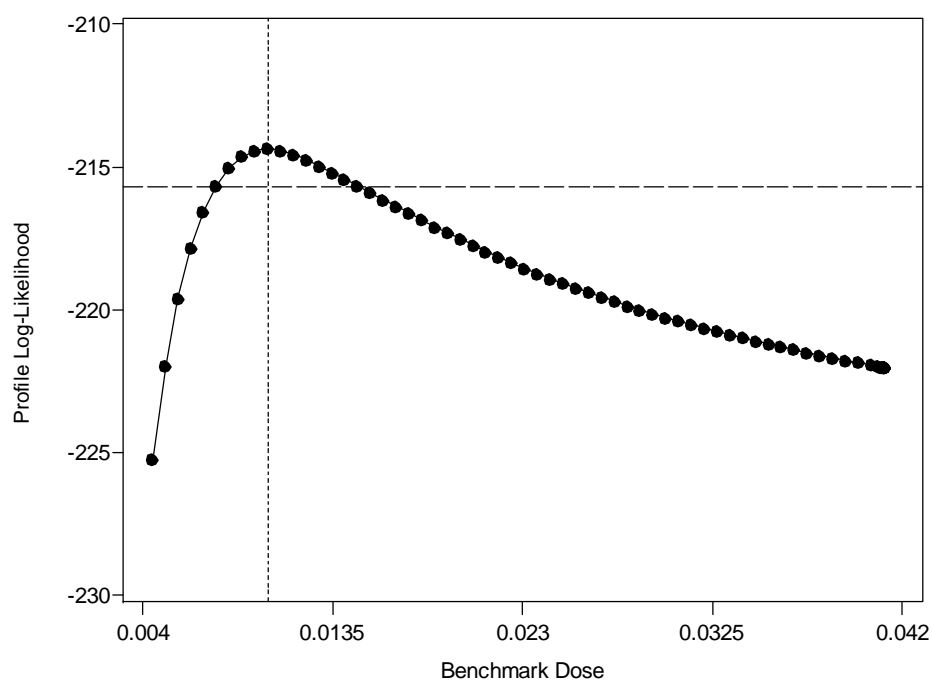
Incidental Extra Risk at 104 Weeks	Model	BMD	90% Confidence Bounds (Lower 95%, Upper 95%)
1.0E-06	Estimated (BMDS)	1.0275E-006	(7.2427E-007, 1.6408E-006)
	Simulation ("True")	3.0763E-003	
1.0E-05	Estimated (BMDS)	1.0275E-005	(7.2427E-006, 1.6408E-005)
	Simulation ("True")	3.0763E-002	
1.0E-04	Estimated (BMDS)	1.0275E-004	(7.2751E-005, 1.6408E-004)
	Simulation ("True")	3.0765E-001	
1.0E-03	Estimated (BMDS)	1.0280E-003	(7.2615E-004, 1.6413E-003)
	Simulation ("True")	3.0779E+000	
1.0E-02	Estimated (BMDS)	1.0327E-002	(7.3066E-003, 1.6467E-002)
	Simulation ("True")	3.0918E+001	
1.0E-01	Estimated (BMDS)	1.0826E-001	(7.6388E-002, 1.7049E-001)
	Simulation ("True")	3.2412E+002	

B1.1.3. Plots of Profile Log-Likelihood Functions

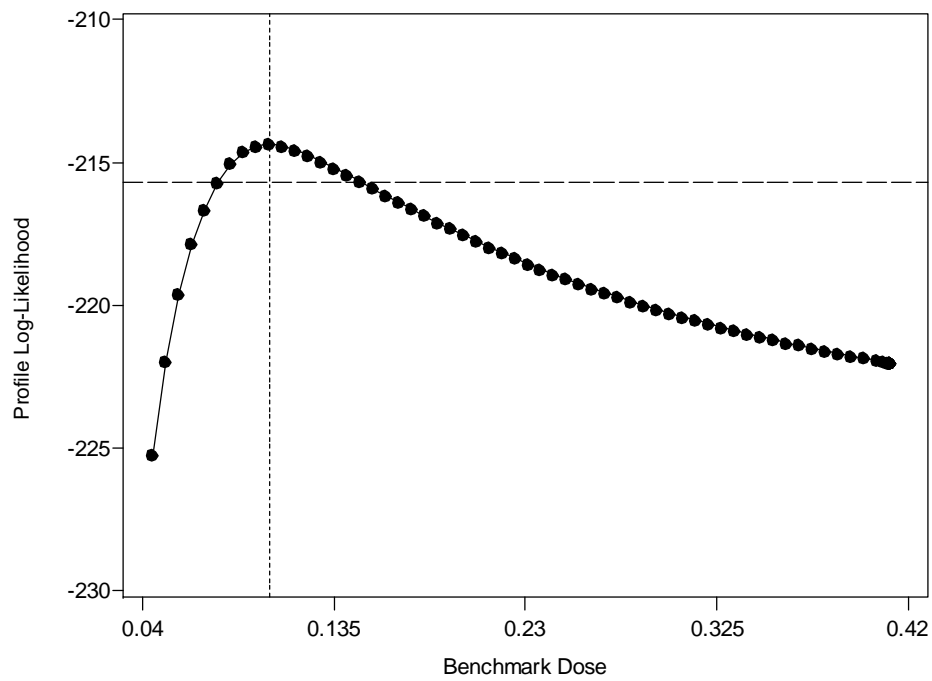
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



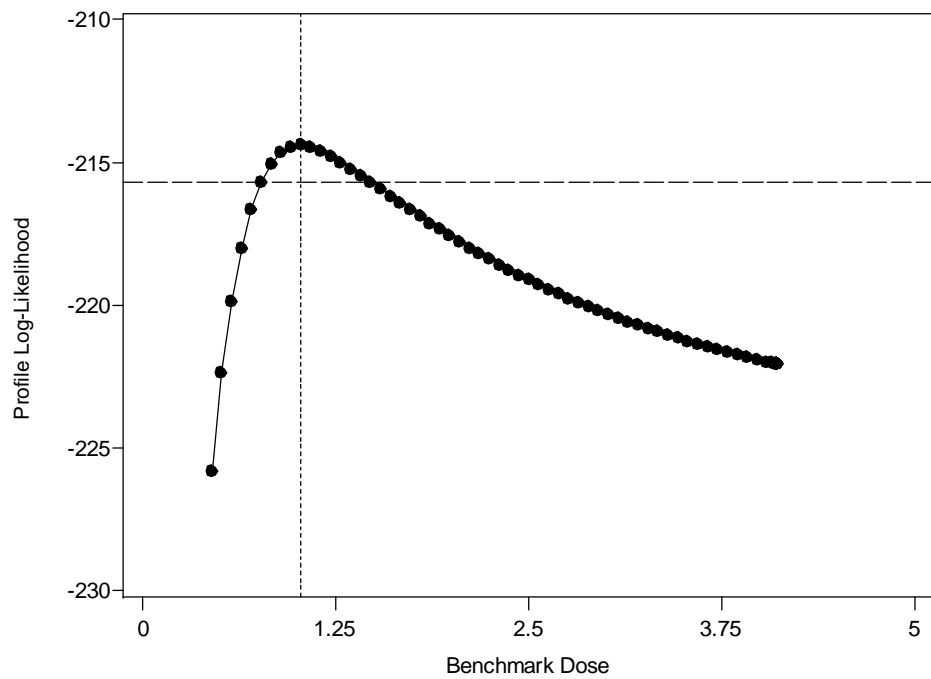
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



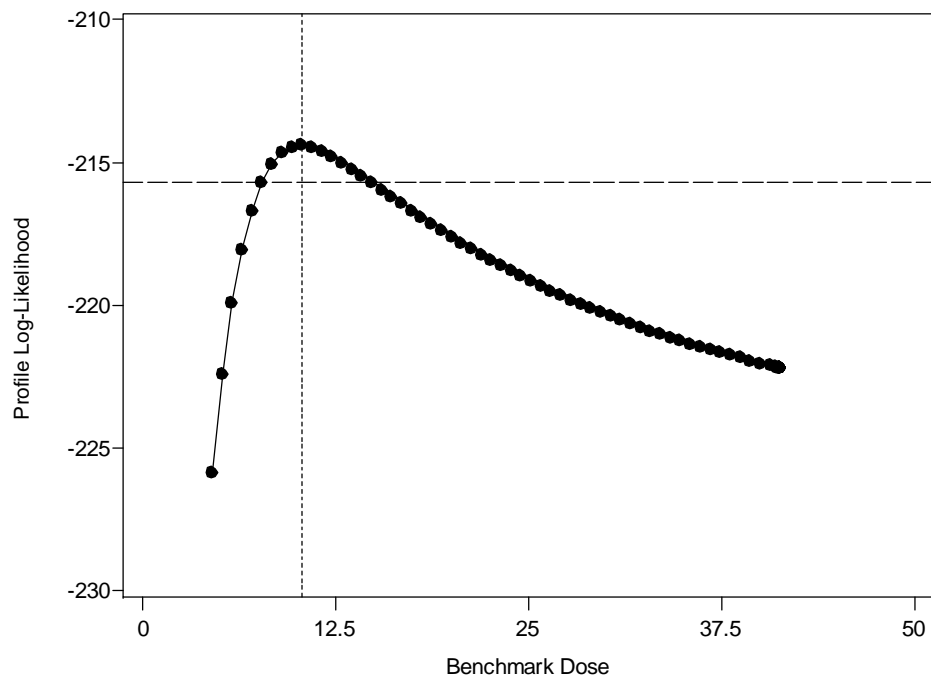
Incidental Extra Risk = 1.0E-04 at 104 Weeks



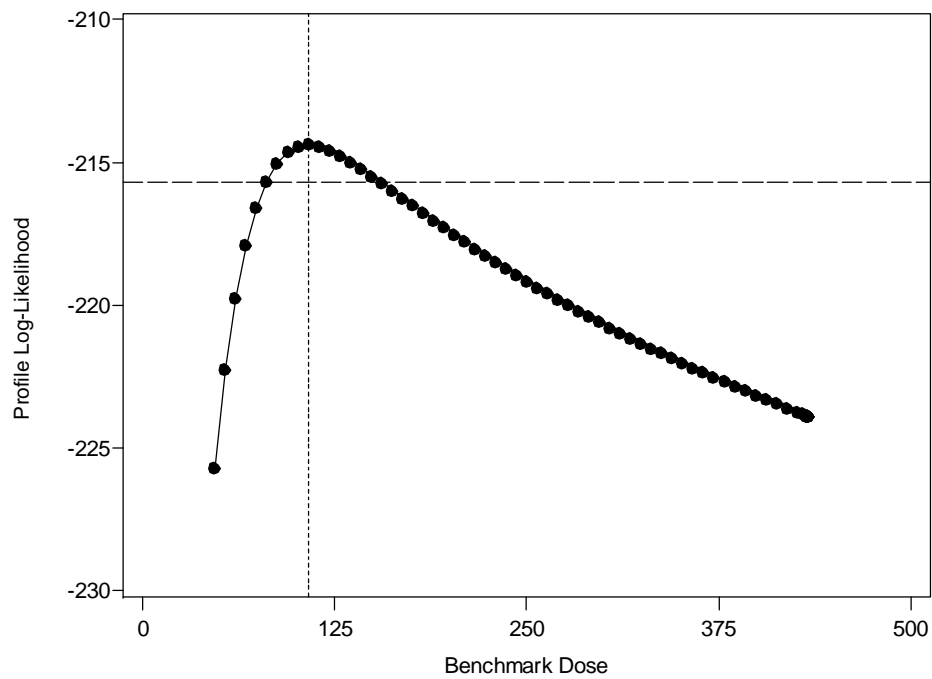
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



B1.2. 1-Stage Model

B1.2.1. Model Parameters

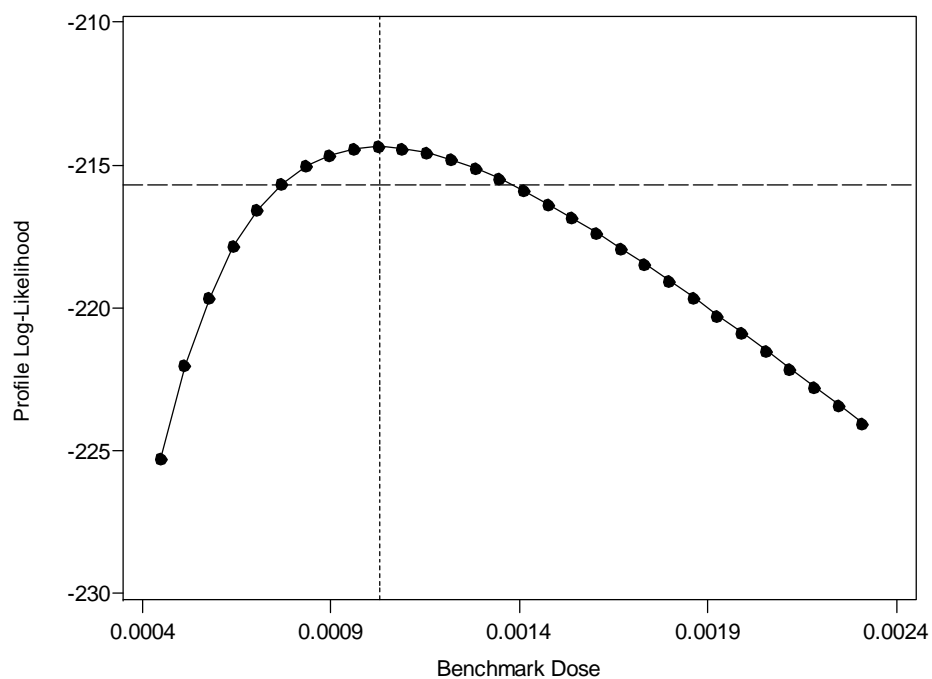
Parameters	MLE (Log-Likelihood = -2.143563E+002)	Simulation Model
c	6.223897E+000	4.86
t_0	1.626028E+001	23
β_0	0.000000E+000	1.03E-011
β_1	2.719038E-013	1.54E-010

B1.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

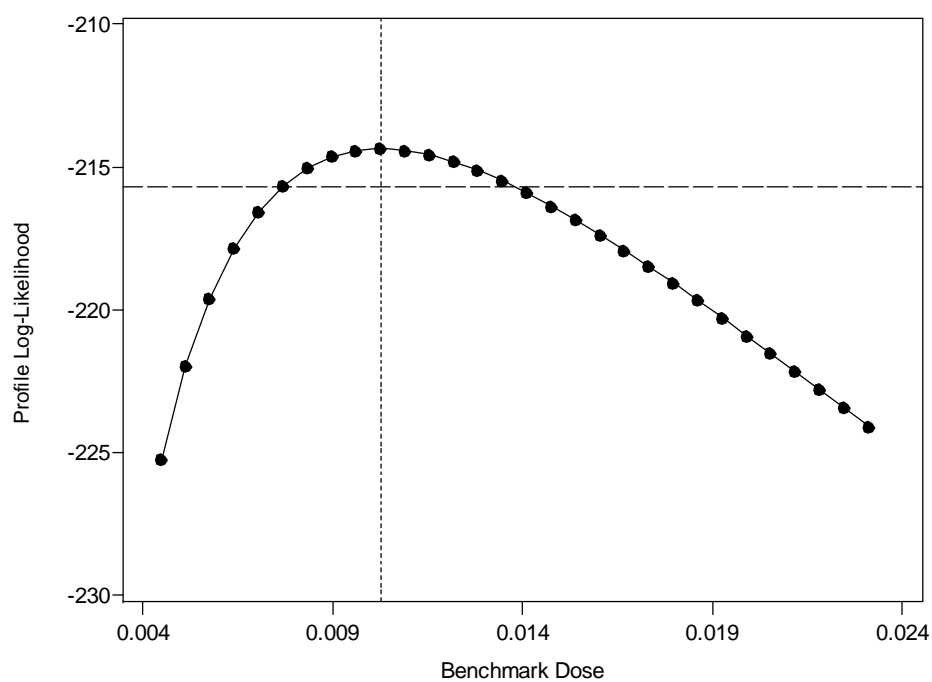
Incidental Extra Risk at 104 Weeks	Model	BMD	90% Confidence Bounds (Lower 95%, Upper 95%)
1.0E-06	Estimated (BMDS)	1.0275E-006	(7.2427E-007, 1.4654E-006)
	Simulation ("True")	3.0763E-003	
1.0E-05	Estimated (BMDS)	1.0275E-005	(7.2427E-006, 1.4654E-005)
	Simulation ("True")	3.0763E-002	
1.0E-04	Estimated (BMDS)	1.0275E-004	(7.2751E-005, 1.4655E-004)
	Simulation ("True")	3.0765E-001	
1.0E-03	Estimated (BMDS)	1.0280E-003	(7.2615E-004, 1.4647E-003)
	Simulation ("True")	3.0779E+000	
1.0E-02	Estimated (BMDS)	1.0327E-002	(7.3142E-003, 1.4723E-002)
	Simulation ("True")	3.0918E+001	
1.0E-01	Estimated (BMDS)	1.0826E-001	(7.6754E-002, 1.5384E-001)
	Simulation ("True")	3.2412E+002	

B1.2.3. Plots of Profile Log-Likelihood Functions

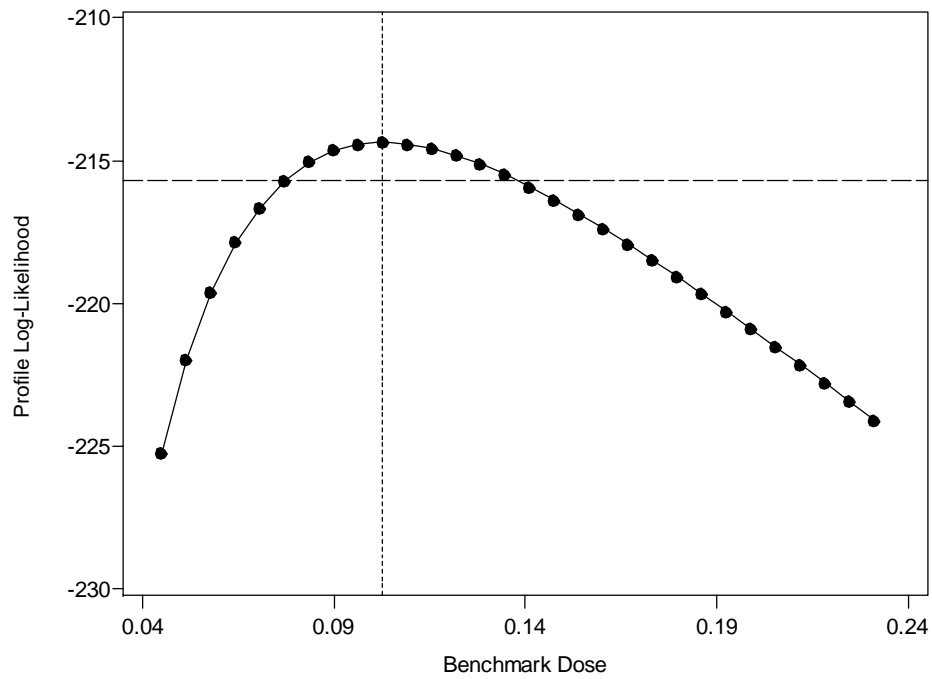
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



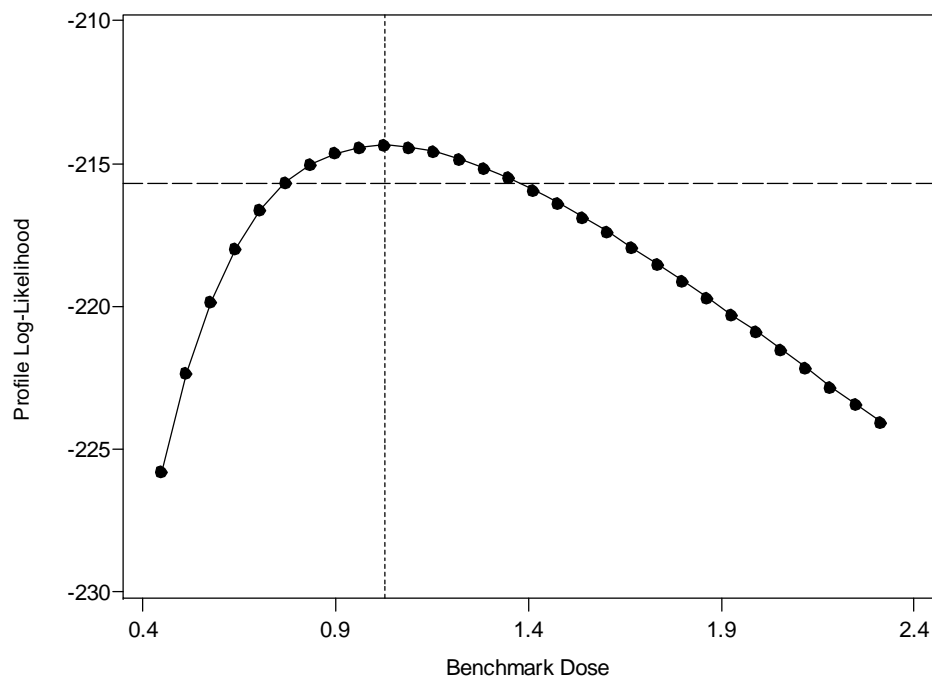
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



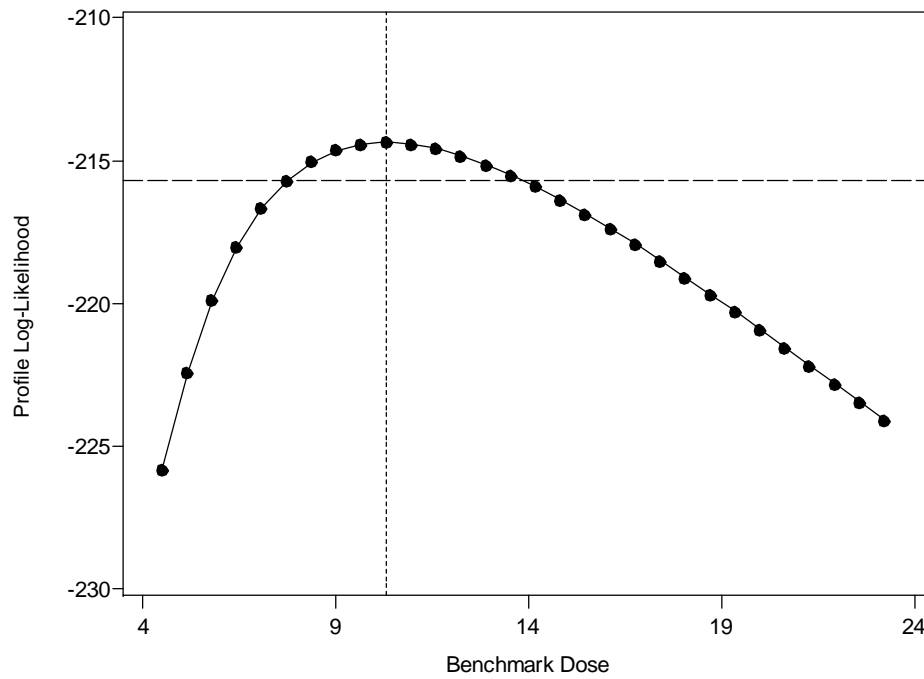
Incidental Extra Risk = 1.0E-04 at 104 Weeks



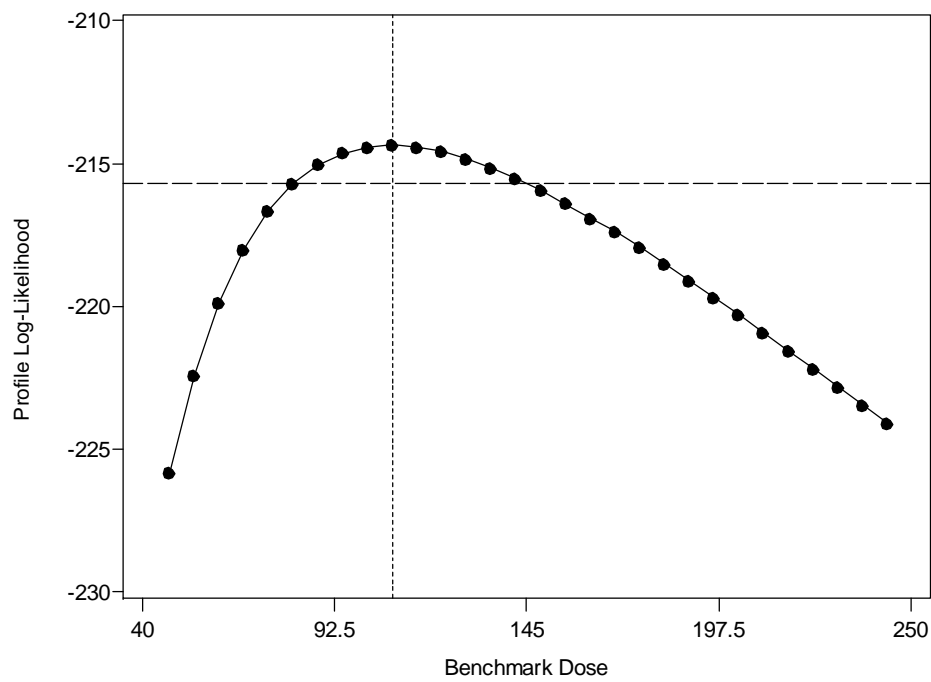
Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



B2. Simulated Dataset 2 (sim11jun07b)

B2.1. 3-Stage Model

B2.1.1. Model Parameters

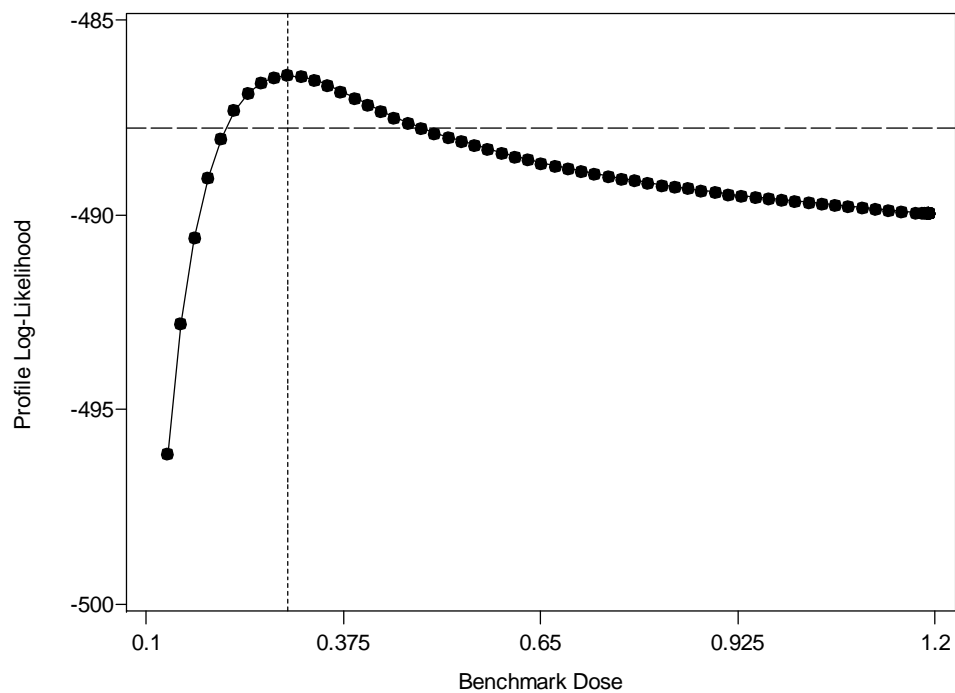
Parameters	MLE (Log-Likelihood = -4.864149E+002)	Simulation Model
c	6.080689E+000	5
t_0	1.864246E+001	23
β_0	5.005135E-013	1.07E-010
β_1	1.822926E-015	2.53E-013
β_2	0.000000E+000	0
β_3	0.000000E+000	0

B2.1.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

Incidental Extra Risk at 104 Weeks	Model	BMD	90% Confidence Bounds (Lower 95%, Upper 95%)
1.0E-06	Estimated (BMDS)	2.9804E-004	(1.9832E-004, 5.8133E-004)
	Simulation ("True")	1.4007E+000	
1.0E-05	Estimated (BMDS)	2.9804E-003	(1.9828E-003, 5.8133E-003)
	Simulation ("True")	1.4007E+001	
1.0E-04	Estimated (BMDS)	2.9806E-002	(1.9830E-002, 5.8133E-002)
	Simulation ("True")	1.4008E+002	
1.0E-03	Estimated (BMDS)	2.9819E-001	(1.9846E-001, 5.8138E-001)
	Simulation ("True")	1.4014E+003	
1.0E-02	Estimated (BMDS)	2.9954E+000	(1.9929E+000, 5.8199E+000)
	Simulation ("True")	1.4078E+004	
1.0E-01	Estimated (BMDS)	3.1402E+001	(2.0962E+001, 5.9029E+001)
	Simulation ("True")	1.4758E+005	

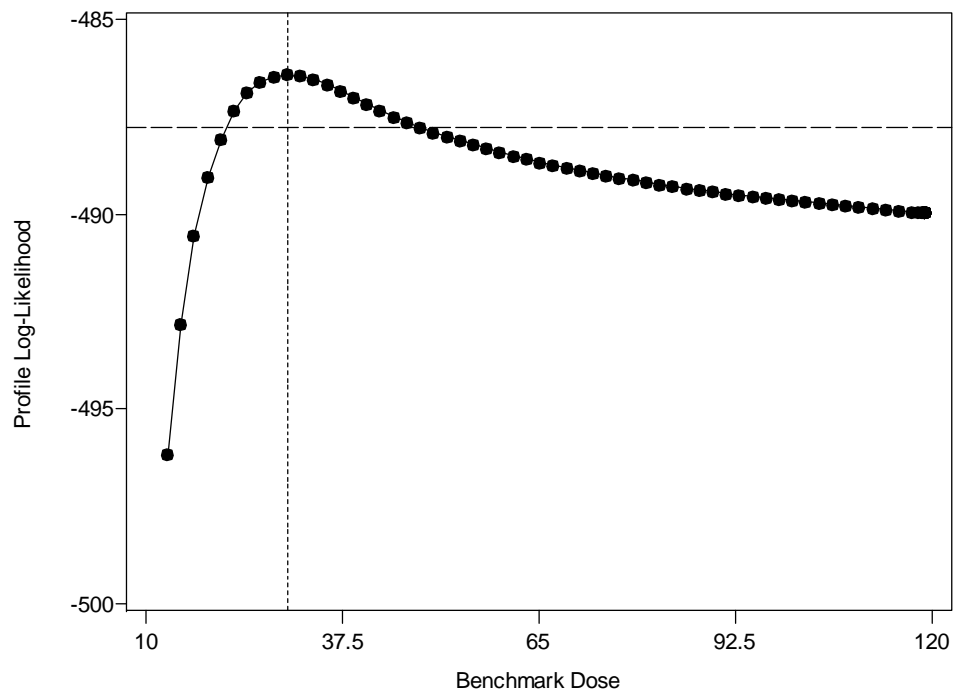
B2.1.3. Plots of Profile Log-Likelihood Functions

Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks

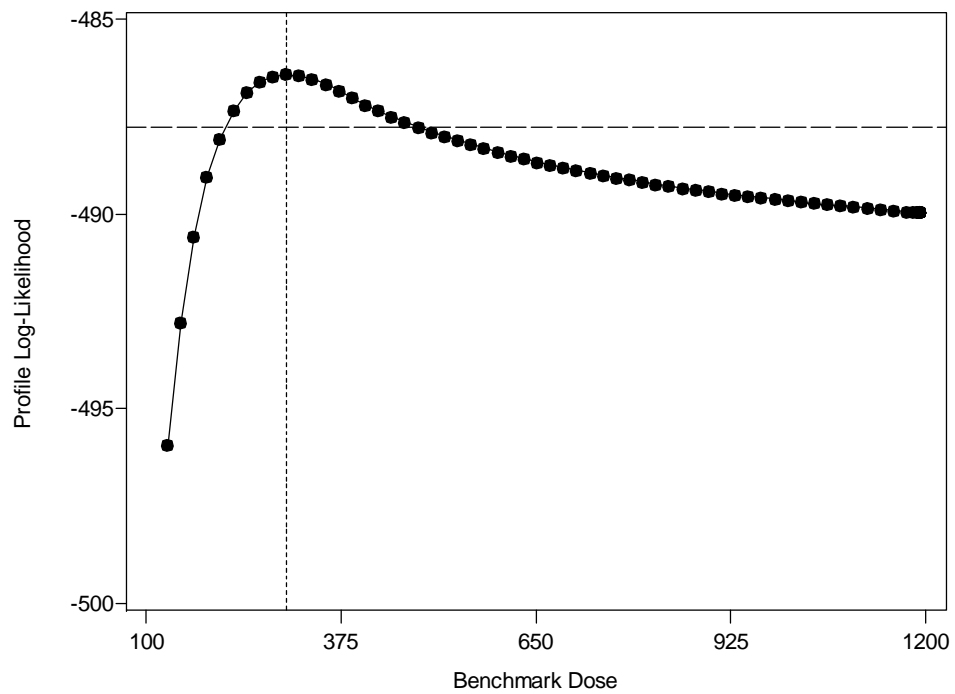


Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks

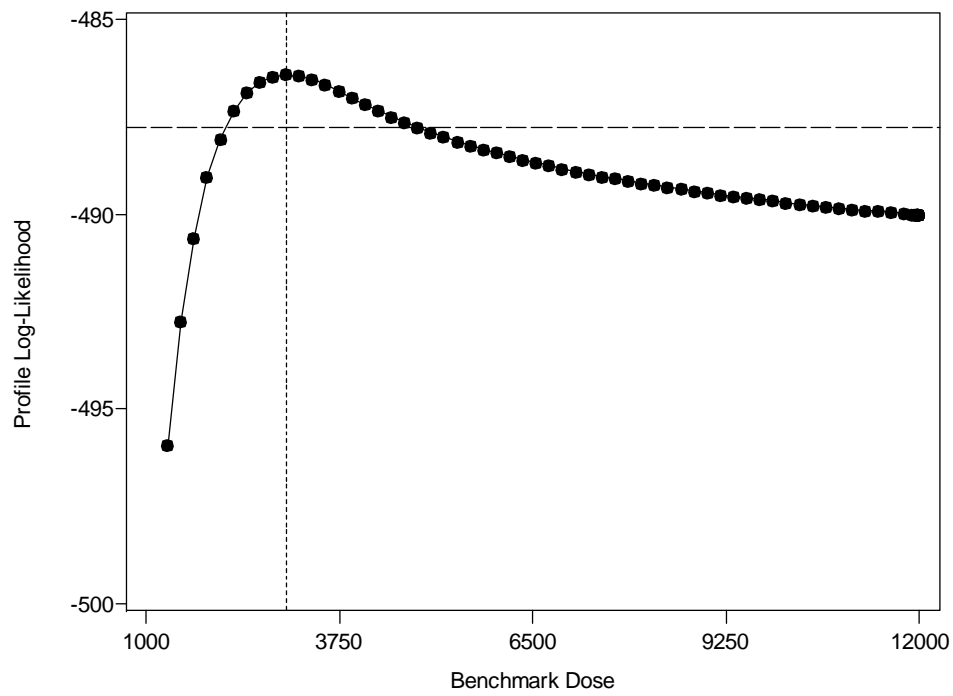
Incidental Extra Risk = $1.0\text{E-}04$ at 104 Weeks



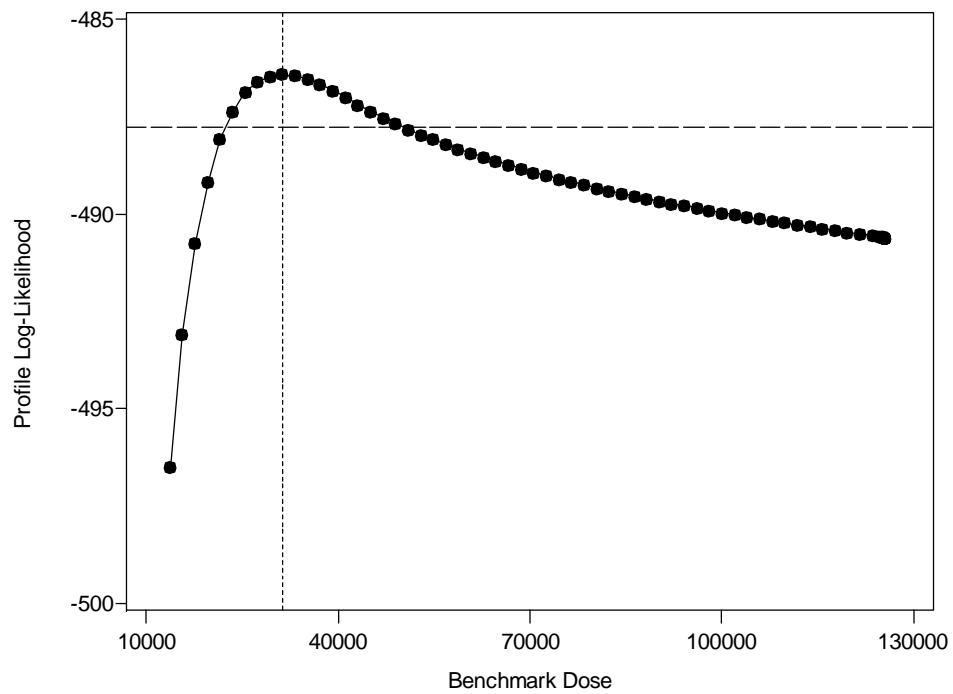
Incidental Extra Risk = $1.0\text{E-}03$ at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks



B2.2. 1-Stage Model

B2.2.1. Model Parameters

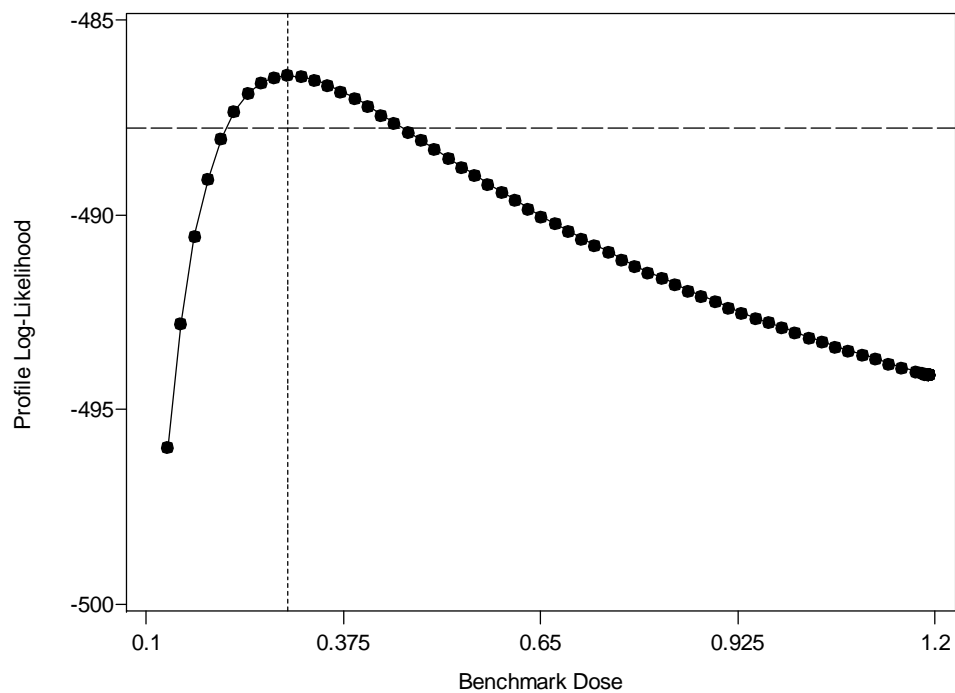
Parameters	MLE (Log-Likelihood = -4.864149E+002)	Simulation Model
c	6.080689E+000	5
t_0	1.864246E+001	23
β_0	5.005141E-013	1.07E-010
β_1	1.822929E-015	2.53E-013

B2.2.2. BMD and Profile Likelihood 90% Confidence Interval (95% Lower and Upper Bounds)

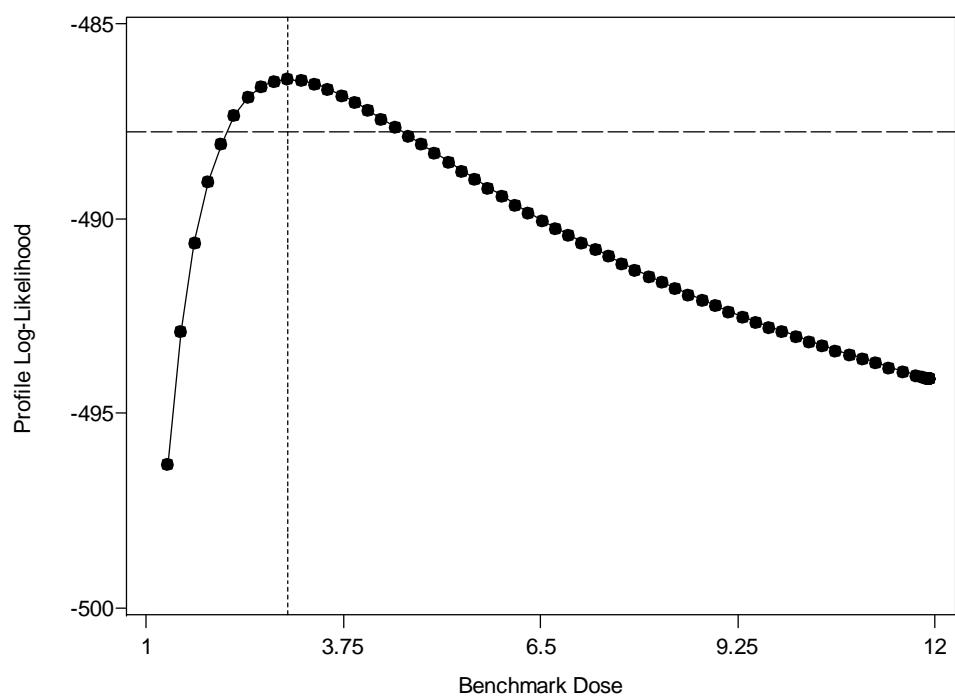
Incidental Extra Risk at 104 Weeks	Model	BMD	90% Confidence Bounds (Lower 95%, Upper 95%)
1.0E-06	Estimated (BMDS)	2.9804E-004	(1.9829E-004, 5.0479E-004)
	Simulation ("True")	1.4007E+000	
1.0E-05	Estimated (BMDS)	2.9804E-003	(1.9828E-003, 5.0479E-003)
	Simulation ("True")	1.4007E+001	
1.0E-04	Estimated (BMDS)	2.9806E-002	(1.9829E-002, 5.0482E-002)
	Simulation ("True")	1.4008E+002	
1.0E-03	Estimated (BMDS)	2.9819E-001	(1.9838E-001, 5.0501E-001)
	Simulation ("True")	1.4014E+003	
1.0E-02	Estimated (BMDS)	2.9954E+000	(1.9938E+000, 5.0734E+000)
	Simulation ("True")	1.4078E+004	
1.0E-01	Estimated (BMDS)	3.1402E+001	(2.0892E+001, 5.3186E+001)
	Simulation ("True")	1.4758E+005	

B2.2.3. Plots of Profile Log-Likelihood Functions

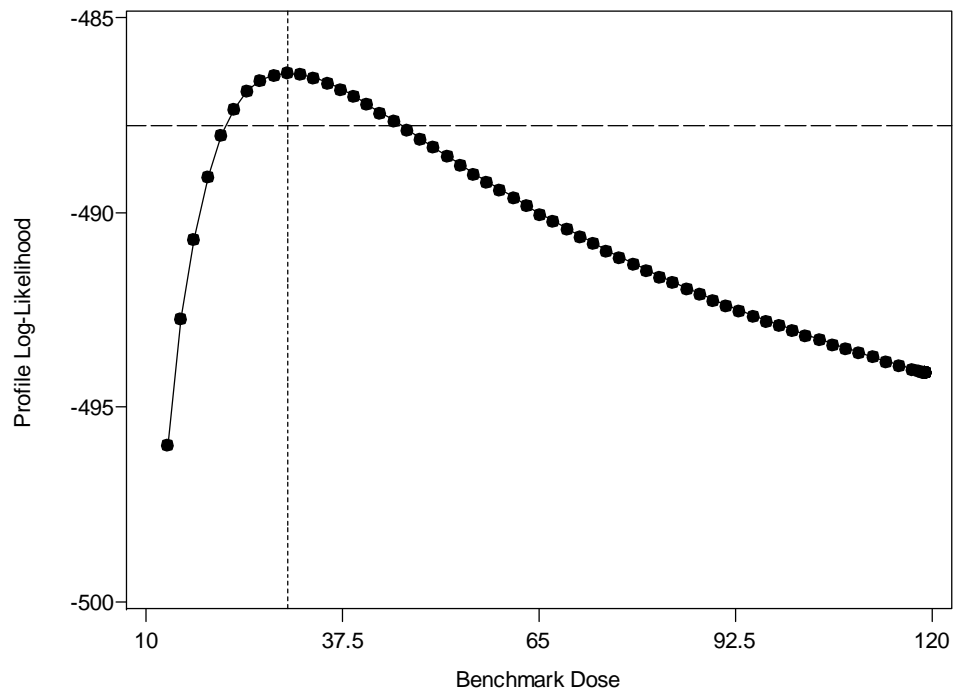
Incidental Extra Risk = $1.0\text{E-}06$ at 104 Weeks



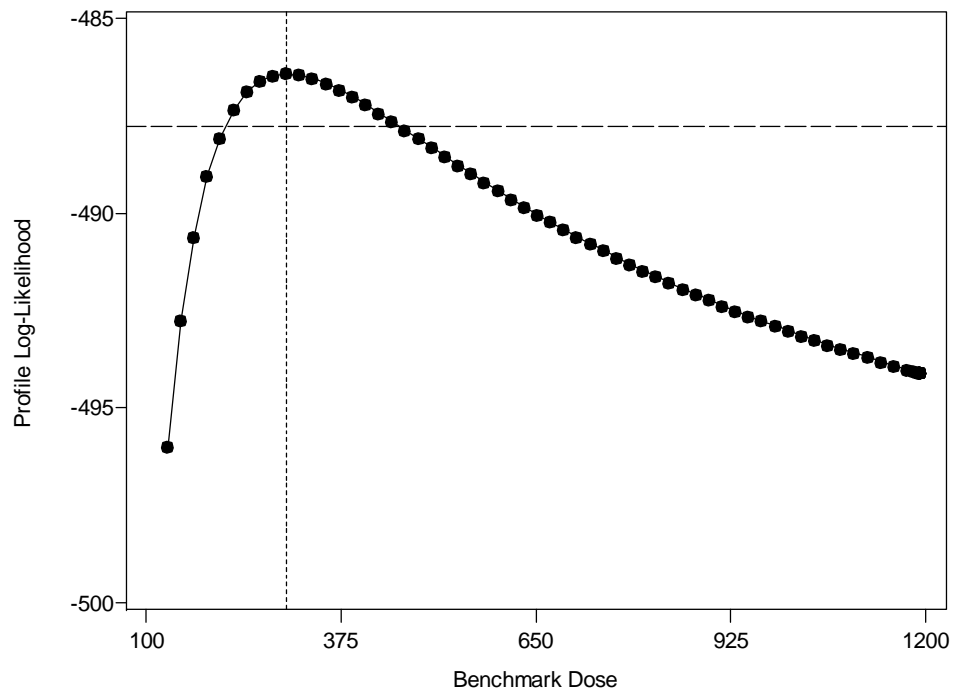
Incidental Extra Risk = $1.0\text{E-}05$ at 104 Weeks



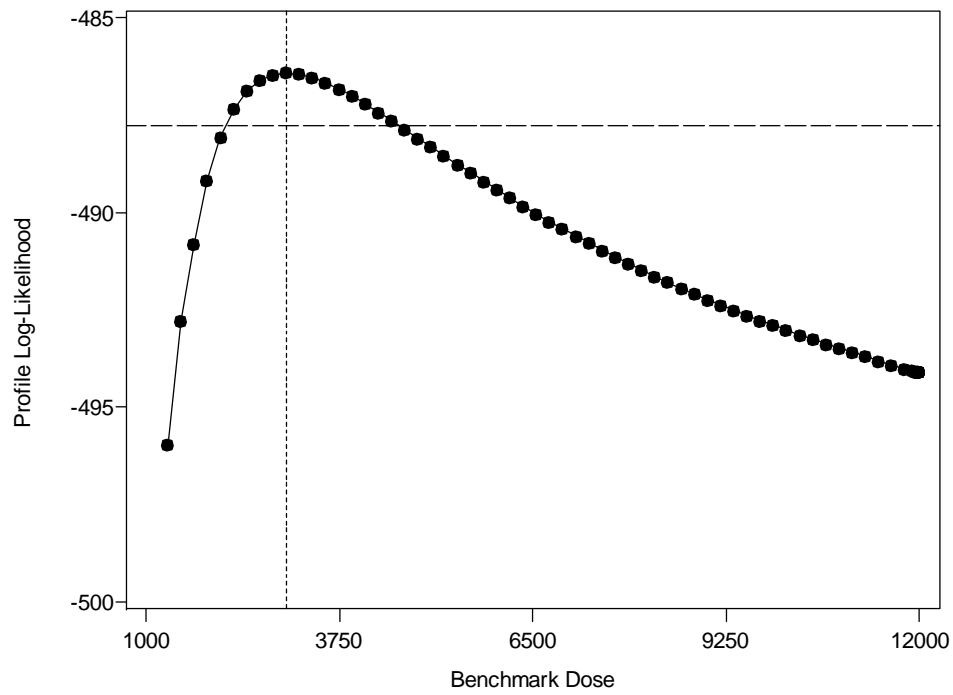
Incidental Extra Risk = 1.0E-04 at 104 Weeks



Incidental Extra Risk = 1.0E-03 at 104 Weeks



Incidental Extra Risk = 1.0E-02 at 104 Weeks



Incidental Extra Risk = 1.0E-01 at 104 Weeks

