Peer Review of EPA's Draft Document
EPA/NCEA Exponential Continuous Models, External Review Draft Version 1.1

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9/10/07

Review of EPA Document:
"Exponential Continuous Models: External Draft Version 1.1"

David W. Gaylor, Ph.D
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General Impressions

The information in the Document appears to be accurate and presented clearly. The Document is comprehensive and concise. The Document supports the comparability of the PROAST modeling system, developed by Dr. Wout Slob of the Netherlands Environmental Protection Agency, and the U.S. EPA Benchmark Dose Software (BMDS) program for estimating dose-response relationships and for deriving confidence bounds on estimates of benchmark doses (BMDLs) for specified responses (BMRs) for nested exponential continuous models. Flexible exponential models allowing dose raised to a power and allowing asymptotic values were evaluated.

Charge Questions

1. Clarity of Report and Model Output: Are documentation and model output associated with the EPA exponential models as clear as their corresponding PROAST exponential models and consistent with that for existing BMDS continuous models?

> Yes. The output format is similar to the current BMDS program which will make it easy for users familiar with BMDS to utilize the new nested exponential continuous models feature.

2. Adequacy of Testing Methods and Results: The testing process should insure that the EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models.

(a) Is the record provided in the development and testing reports sufficient to document the testing methods used and results of software testing?

> Yes. The primary criterion is satisfied that BMDS provides estimates of BMD and BMDL that are similar to PROAST.

(b) Have appropriate aspects of the EPA exponential models been tested?

> Yes. The test cases include an exponential model that is only slightly curved as well as models with moderate curvature representative of actual situations. Also, the test cases include examples with both low and high coefficients of variation.

(c) Do the test results indicate that the EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models?

Yes. However, it is disconcerting for Model 4 that the estimates of b and c differ between PROAST and BMDS (Page 21, Table 4). Also, for Model 5 it is discomforting that the estimates for b, c, and d differ between PROAST and BMDS. However, the BMD estimates are similar between these two procedures. Can any explanation be offered?

3. Other Issues: Are there any aspects of software development and testing, or model documentation, or reporting of model results that give you special cause for concern?

Page 12, Table. The example is referring to negative exponential models. There should be a minus sign in front of the BMD formulas for each of the models.

PROAST only considers data that are normally distributed. Since many biological effects appear to be approximately log-normally distributed, some evaluation of BMDS should be made for this case. Perhaps this can be investigated utilizing computer simulations.

Review by
Peter R. McClure, Ph.D., DABT

Peer Review Comments on
EPA/NCEA "Exponential Continuous Models, External Review Draft Version 1.1"

Peter R. McClure
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September 21, 2007

I. GENERAL IMPRESSIONS

The document provides 1) informative rationale and background for adding code to the BMDS that will fit nested exponential models to continuous variable dose-response data, 2) descriptions and explanations of the output of the new BMDS code, and 3) description and interpretation of the results of testing the limits and reliability of the new BMDS code by comparing outputs for three data sets with outputs from independent codes applied to the same data sets (PROAST code for constant variance models and Excel code for non-constant variance models).

Section 5 would benefit from some rewriting to more clearly describe the development of the Excel reference code and the rationales for using the selected test data sets. Testing the new BMDS code against the reference codes with additional data sets of varying characteristics (e.g., different shapes of the dose-response and dose-variance curves) may provide more comprehensive testing of the new BMDS code.

II. RESPONSE TO CHARGE QUESTIONS

1. Clarity of Report and Model Output Are documentation and model output associated with the EPA exponential models as clear as their corresponding PROAST exponential models and consistent with that for existing BMDS continuous models?

Comments: Yes, the model outputs from the new code are clear and consistent with output for existing BMDS continuous models. The PROAST output does not appear (from Appendices H, I, and J) to include some of the features of the BMDS code (e.g., statistical tests of fit and BMD/BMDL calculations).

Sections 1-4 of the report read well, but Section 5.1 needs to be rewritten to more clearly explain testing methods. In particular, the development of the independent reference code (Excel code) for fitting non-constant variance models needs to be more clearly described (see questions and comments under Specific Observations, items 13 and 14) and rationales for selecting the data sets used in the testing should be more clearly articulated. I have made suggestions for revisions to Sections 5.3 and 5.4. that, to my mind, more concisely describe and interpret the test results data closer to the data tables and separate the overall testing conclusions from the data descriptions and interpretations.

2. Adequacy of Testing Methods and Results: The testing process should ensure that the EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models.

(a) Is the record provided in the development and testing reports sufficient to document the testing methods used and results of software testing?

Comments: Yes, from the report I have some confidence that output from the BMDS exponential model code is similar to output from the PROAST code for fitting constant variance models and output from the Excel code for fitting non-constant variance models, at least with the three datasets tested. It may be useful to use other data sets with other characteristics (such as different shapes of the dose-response curve or dose-variance curve) to compare the limits and reliability of the BMDS code with the reference codes.

(b) Have appropriate aspects of the EPA exponential models been tested?

Comments: Rationales for selecting the testing data sets should be provided. Fitting model 4 to Data Set 1 was problematic in that convergence of the fitting was not achieved by the BMDS code and the reference codes. From reading the report, however, I am not sure why convergence problems were encountered. The change in mean response looks almost linear when plotted, but the standard deviations are changing more at the higher doses than at the lower doses. Could this apparent non-linearity be the source of the problem?

Again, testing with other data sets that challenge the fitting and/or calculation programs may increase confidence that output from the BMDS code is reliable and accurate.

(c) Do the test results indicate that EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models?

Comments: Yes, but see my comments and questions under Specific Observations, items 13 and 14.

3. Other Issues: Are there any aspects of software development and testing, or model documentation, or reporting of model results (*.out file) that give you special cause for concern? If so, please describe you concerns and recommendations.

Comments: No other issues at this time. When I use the software, I will better be able to assess whether the interpretation text for the statistical tests (Tables 11, 12, 13) make sense to a toxicologist with some statistical training and fairly extensive experience in using dose-response models to derive toxicity values such as RfDs, RfCs, and cancer slope factors. Not being a statistician, I cannot comment on the appropriateness of the statistical tests.

III. SPECIFIC OBSERVATIONS

1. P. 7 second equation: s^2(dose) = exp{1alpha+rho*ln(m(dose))}---- there is no mention of what "m" is in the explanatory text. If this is not a typographical error, please provide explanation.

2. P. 7 explanatory text for first and second equations: Replace "s^2(dose) is the variance for the normal distribution, as a function of dose" with ""s^2(dose) is the estimate of the variance for the normal distribution (σ^2), as a function of dose"

3. P. 8 footnote 1: the additional term is designated as "-ln(2p)*SN(i)/2"---- please specify the terms "p", "S" (should this be lower case????), and "N(i)". Also, I found that the footnote to Table 4 on page 22 noted that this additional term is "Nln(2p)/2 --- why the discrepancy?

4. P. 9 several places in text: replace "a" with "α" when referring to the confidence level

5. P. 10 second line of last paragraph: replace "my" with "may"

6. P. 11 last 2 sentences continuing to p. 12: suggested revision: The BMD estimate for Model 1 does not exist. Model 1 is simply the specification of a constant mean model, which is called Model R ("Restricted") in the BMDS implementation of the exponential models, as it is in all the other BMDS continuous models.

7. P. 12 equations in Table: Please check algebra for all four of the equations. For Model Number 2, I come up with BMD = -(1/b) * ln{BMR/a}. The negative sign is missing in the table.

8. P. 13-16 "Running the Model from a Windows Command Prompt": I read through this section, and it seemed to make sense, but I did not run the exponential models.

9. P. 17, first sentence in first paragraph after Table 1: Suggested revision--- Appendix B contains the output file produced by the BMDS code for fitting the nested exponential models to this data set.

10. P. 17, second *sentence in last paragraph.* Add the following parenthetical statement to the end of the sentence: "(see Section 2 for more on model nesting)". I felt I needed to go back and remind myself how nesting of models was being used in this document -- this addition will aid the reader to find where the issue has been discussed previously in the document.

11. P. 19, first sentence: Suggested revision: Two sources of estimates and output values were used as the basis for testing the current BMDS code for fitting the nested exponential models ("BMDS exponential model code") to three datasets (see Table 1 in Section 4, and tables 2 and 3 in Section 5.2). NOTE: please be consistent throughout the text when referring to the "current code" -- different terms are used at different places in the document – this is confusing to me.

12. P. 19, third paragraph: Suggested revision: The PROAST software is limited for the purposes of testing all options included in the current BMDS exponential model code: 1) it fits only constant variance forms of the nested exponential models; and 2) it does not compute BMD values with BMRs defined in terms of standard deviation.

13. P. 20, fourth paragraph, second part beginning with the sentence, "The constant variance version of the fit via the Excel……." I am confused by this text, as I will try to illustrate. Please modify accordingly.

a. *"The constant variance version…."* ---- It is not clear what is meant by "the Excel spreadsheet returned estimates that were confirmed by the PROAST software runs." Is it meant that model parameters and estimates of log-likelihoods and BMDs for constant variance models from the Excel and PROAST codes were identical, or similar? I could not find anyplace in the document, which showed a comparison of the PROAST code outputs with EXCEL code outputs. If I understand correctly, Tables 4, 5, and 6 could be supplemented (add a column to each) with model parameters and estimates of log-likelihood and BMD from the Excel code to document that the PROAST code "confirmed" the Excel code.

b. *"Although the spreadsheet maximum likelihood estimates for the non-constant variance models have not been confirmed to be absolutely correct (within rounding error and machine precision),"* It is not clear to me how you would confirm that the Excel code gives "absolutely correct" model parameters and estimates of log-likelihoods and BMDs.

c. *"graphical comparison of the observed and predicted means and standard deviations so obtained suggested that the estimates derived were reasonable."* I think that this comparison does not indicate that the model parameters and estimates of log-likelihood and BMDs from the Excel code are correct. What do you mean by "reasonable"?

d. *"Moreover, they appeared to be generally robust to perturbations of those estimates; when the estimates were perturbed from their final values by varying amounts, they tended to return to those values when the likelihood was remaximized."* This check of the Excel code and its "Solver" function appears to me to be more useful than the graphical comparison. Some examples of this perturbation protocol should be added to document the statement that "they tended to return to those values when the likelihood was remaximized."? Is it meant by "tended to return" that similar, but not identical, values were obtained after the perturbations? If so, what criteria for similarity was used – within 1%, 10% change?

14. P. 20, last paragraph: Suggested revision: A second (previously developed) Excel code that only calculates the log-likelihoods for the models designated as A1, A2, A3, and R in the standard BMDS code and output was used to confirm the output of the current BMDS exponential model code. Previous use of the second Excel code has confirmed that the likelihood calculations are correct.

Query: How was it confirmed that the likelihood calculations were correct? Could that same process be applied to test the correctness of the model parameters and likelihood and BMDs calculation of the "current BMDS exponential model code" ?

15. P. 20. Table 3 title: Third Dose-Response Data Set for Testing (test3.(d))

16. P. 21-27 Section 5.3 Testing Results: The testing results are presented in tables in this section and summary text is in Section 5.4. Concise summary text close to the data tables would aid the reader. Discuss the results for the constant variance models first, then those for the non-constant variance models. The overall conclusions about the test results (which can be very short) can then be presented in Section 5.4.

Example for Suggested Title Changes for Tables: *Table 4. Data Set 1 Constant Variance Model Parameters and Calculation of BMD and Likelihood Values: PROAST, BMDS, EXCEL Codes* --- see previous comments about adding EXCEL column for Tables 4, 5, and 6).

NOTE: Tables 8-10 pages 24-27: I think BMD (01), BMD(10) and BMDL(10) should be noted as BMD(0.1), BMD(1.0), and BMDL(1.0).

Suggested Revision:

Constant Variance Model Tests: Comparison of PROAST and BMDS Codes

The runs of the R version of PROAST are summarized via screen shots of the modeling results (Appendices H, I, and J for test 1, test 2, and test 3, respectively). Tables 4-6 summarize the comparisons of constant variance model parameters and likelihood and BMD calculations from the PROAST and BMDS codes. The BMD values shown are for a BMR defined as 1 standard deviation away from the control mean.

For Data Set 1, estimated values for parameters of constant variance models 2 (variance, a, and b) and 3 (variance, a, and b) from the PROAST and BMDS codes were similar and values of log-likelihoods and BMDs were identical (Table 4). However, model parameters of models 4 and 5 from the PROAST and BMDS codes showed some differences. For example, for model 4, the PROAST and BMDS codes arrived at parameter "c" values of 62.29153 and 44.250414, respectively, identical log-likelihood values, and similar BMD values (210.907 and 210.268). For model 5, respective values for parameter "c" were 3.459957 and 38.652488, log-likelihood values were -152.848 and -152.862, and BMDs were 215.610 and 216.959. The PROAST code failed to converge with model 4, but the BMDS code did not report any difficulty in convergence.

For Data Set 2 (Table 5) and 3 (Table 6), constant variance model parameters were similar and values of log-likelihoods and BMDs were identical from the PROAST and BMDS codes.

BMDL calculations with the current BMDS exponential model code were compared with those made with the Excel exponential model code (Table 7). The BMDL values were identical (to six significant digits) for all model and Data Set combinations with the exception that the BMDS reported an error in the calculation for Model 4 with Data Set 3. The message relates to the

process by which the BMDL guesses are stepped down by multiples of 0.9 until a lower bond on the true BMDL is found. In this instance, the step-down process terminated before such a bound could be located.

Non-Constant Variance Model Tests: Comparison of Excel and BMDS Codes

The output files from the BMDS code shown in Appendices B (Data Set 1), C (Data Set 2), and D (Data Set 3) give BMD estimates for a BMR defined as one standard deviation from the control mean (Specified Effect = 1.0; BMD(1.0)). The BMDs when the Specified Effect = 0.1 [BMD(0.1)] were obtained from separate runs and output files, which were identical to the ones shown in Appendices B, C, and D, except for the BMD estimates. Non-constant variance model parameters, log-likelihood values, and BMD and BMDL values for Data Sets 1, 2, and 3 are shown in Tables 8, 9, and 10, respectively.

For Data Set 1, estimated values for parameters of non-constant variance models 2, 3, and 5 from the EXCEL and BMDS codes were similar, as were values of log-likelihoods and BMDs (Table 8). With model 4, the BMDS code gave a convergence warning, and the Excel code terminated without apparently achieving a maximum likelihood result. For Data Set 2 (Table 9) and 3 (Table 10), model parameters and estimates of log-likelihood and BMDs from the Excel and BMDS codes were similar or identical, except for the few cases for which the BMDS reported a computational error in calculating the BMDL. In these instances, the code had completed a step-down procedure and had begun to "fine-tune" the estimates of the BMDL; the last value calculated before the error message in the output files is reflected in the tables. The error is related to the fact that for Models 4 and 5, the mean values of the observations must fall between a and a*c. For some combinations of a, ln(alpha), and rho, which define the value of the BMR, that BMR falls outside the range from a to a*c. The optimizing function is not correctly recognizing these as cases for which no dose can give a mean response equal to the BMR, and the BMDL estimation terminates.

17. P. 30-31. Interpretation of Testing Results: If suggestions for revising Section 5.3 are acceptable, consider condensing Section 5.4 as follows.

5.4 TESTING CONCLUSIONS

Overall, it appears that the BMDS exponential model code is fitting the nested exponential models to the three data sets reasonably well. This is true whether the means increase or decrease with increasing dose level or the variance changes or is constant with increasing dose level. Model parameters and calculations of log-likelihood and BMD values from the BMDS exponential model code and independent reference codes were similar, except when convergence problems or confidence limit calculation problems were encountered.

Review by
Cynthia Van Landingham, M.S.

Peer Review Comments on
EPA/NCEA "Exponential Continuous Models, External Review Draft Version 1.1"

Cynthia Van Landingham
ENVIRON International
September 16, 2007

I. GENERAL IMPRESSIONS

In general, the documentation of the exponential models is consistent with the other BMDS documentation for continuous models and the model output is as clear as the corresponding PROAST output provided for this review. However, I much prefer the detailed output provided by the EPA exponential continuous models software to that of PROAST screens provided with the review documentation since the EPA output contains :

- more details about the model's functional form and program settings chosen by the user that define the model,
- testing of the model fit and comparison output both as p-values and as statements accepting or rejecting the test hypotheses based on the p-values, and
- the display of the model parameter estimates, BMDs and BMDLs in a tabular manner.

I find the EPA software's method of capturing of all the related output in one text file a superior method to printing screens or capturing data from screens in accumulating output. The addition of the creation of graph file(s) with graphs of the models fit to the data that are similar to those of the continuous models in the EPA BMDS software would be a welcome addition to the software.

My only criticism of the documentation is that it could be more consistent in its parameter naming and definitions such as in the specification of the equation for the non-constant variance and in the definition of the log-likelihood. Specifically, the alpha parameter in the variance equation is referred to as lalpha, alpha and ln(alpha) in the text and tables and both ln(mean) and log(mean) are used in the text; and, although the output contains the log-likelihood constant, the only mention of this constant in the documentation is in model testing section (Section 5) where the equation and the values for each test data set are given in footnotes.

II. RESPONSE TO CHARGE QUESTIONS

1. Clarity of Report and Model Output: Are documentation and model output associated with the EPA exponential models as clear as their corresponding PROAST exponential models and consistent with that for existing BMDS continuous models?

- Comments: In comparison of the provided output the EPA exponential model output is far better than that on the captured PROAST screens. There is more detail in the EPA output and the output and documentation are consistent with that from the other EPA continuous models. However, I would like to see consistency in the model specifications (e.g. use of ln instead of log and ln(alpha) instead of lalpha in the model definitions and parameter listings. Improvement could be made on the error messages provided in the

output. Messages like - the BMDL does not exist or computational errors are not very informative.

2. Adequacy of Testing Methods and Results: The testing process should ensure that the EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models.

(a) Is the record provided in the development and testing reports sufficient to document the testing methods used and results of software testing?

Comments: Yes I believe so.

(b) Have appropriate aspects of the EPA exponential models been tested?

Comments: The present abilities of the software seem to have been checked. However, from my experience with developing modeling software, I think that only by running a large number of differing datasets through the software provides a completely adequate test.

(c) Do the test results indicate that EPA exponential models are at least as reliable, accurate and clear as the relevant (corresponding) PROAST exponential models?

Comments: Comparison of the PROAST results to the EPA software test results do provide a reliable accurate and clear test corresponding to the same features in the PROAST model as provided in the PROAST output given. Since I am unfamiliar with the PROAST software, more information about it would have given me more confidence that the tests are as reliable as the PROAST models.

3. Other Issues: Are there any aspects of software development and testing, or model documentation, or reporting of model results (*.out file) that give you special cause for concern? If so, please describe your concerns and recommendations.

Comments: For a test that I would have done given the differences between the PROAST and EPA results for dataset test1cg.(d), I reran the EPA software with that dataset after decreasing the relative function convergence and parameter convergence values to 1e-10. The output from this change matched the PROAST log-likelihood, parameter estimates and BMD estimate for Model 5 using test1cg.(d) by. Under these conditions the EPA software gave the same non-convergence error message that the PROAST software did for Model 4 and got a different (from the other EPA run and the PROAST run) parameter, BMD and log-likelihood estimates for that model. With the provided information, I could not confirm or deny that the PROAST model used different convergence criteria. For a complete review, more details about the settings of the PROAST software are needed.

Implementation of the definition of the BMR allowed in PROAST in the EPA software would require further testing of the BMD estimations against PROAST to ensure accuracy relative to the PROAST model.

III. SPECIFIC OBSERVATIONS

In the Model Equations on page 7, 2nd full paragraph, the variance equation includes the variable lalpha. To be consistent the lalpha should be ln(alpha), especially since the tables refer to alpha (tables 4, 5 and 6) or ln(alpha) (Tables 8, 9, and 10). In addition, there should be consistency in the output from the program in respect to alpha and to expression for ln(mean) used in the definition for the non-constant variance and in the tables. Why report the variable as lalpha for the non-constant variance case and alpha for the constant variance case? I find situations like this cause confusion when users are comparing output. Also for clarity, I would include in the text in the first paragraph of the Model Equations section, the obvious fact that when the variance is constant and rho is set to zero, the variance = alpha.

Page 14 Annotation Notes: Please provide the following:

- For Item 6 – number of distinct dose groups – Maximum allowed
- For Item 8 – maximum number of iterations – to what iterations this refers. Iterations in the model fitting, BMD calculation, …? Item 19 gives the type of detail I think is needed here.

Page 18 Parameter Estimation. No initial estimates for parameter c are given for models 4 or 5 although the initial parameter for parameter d for models 3 or 5 is given. Nor is this information provided in the output.

Changes recommended for program output:

- Consistency in the model specifications (e.g. use of ln instead of log and ln(alpha) instead of lalpha in the model definitions and parameter listings.
- printing of the default initial parameter values used for parameters c and d,
- printing of the log-likelihoods in or near the Parameter Estimates table,
- consistent use of alpha as a parameter for both the constant and non-constant variance cases,
- printing of the total log-likelihood (including the constant) in addition to the log-likelihood without the constant for each model in the Likelihoods of Interest table, and
- reporting more specific information when errors occur in the modeling.