Session 2A – Modeling Continuous Data – Questions and Answers

Question 1, Continuous Slide 4: Are the plotted response variances (for each dose group) model independent?
Answer: Yes, the variances plotted by the BMDS graphic software are model independent. This is true for both continuous and dichotomous model plots. Detailed information and references for how dose group variances are plotted can be found in the BMDS Help system or the BMDS user manual (http://epa.gov/ncea/bmds/documentation/BMDS250_manual.pdf).

Question 2, Continuous Slide 9: Do you have any examples of toxic responses that result in a non-normal response distribution within a dose group (i.e., violates the normal distribution assumption)?
Answer: The most common alternative assumption to normal distribution is lognormal distribution. Some prefer to use lognormal distribution as a standard assumption for biological responses because many physical, chemical, biological, toxicological, and statistical processes tend to create random variables that follow Lognormal distributions (Hattis and Burmaster, 1994). However, for BMD analysis purposes, the assumption of normal distribution is generally reasonable, particularly when the BMD is based on a prescribed (e.g., relative or standard deviation) shift in the control mean (Shao et al., 2013). Further, the assumption of normality does not require a constant coefficient of variation and allows for the direct use of group-specific means and standard deviations that are generally reported in the literature, whereas the lognormality assumption implies a constant coefficient of variation and requires an approximate transformation of such summary data to means and standard deviations on a log scale (see discussion of "Unique Options of Exponential Models" in Section 2.6.2.1 of the BMDS User manual).

Question 3, Continuous Slide 12: What if standard deviations are not equal across dose groups?
Answer: Under the normality assumption, all BMDS models have an option to either model the variances (as a power function of the means) or assume constant variance. Under the lognormality assumption, variances can change in the same direction as dose, but not in the opposite direction of dose and the coefficient of variation must be constant.

Question 4, Continuous Slide 12: Why is the estimated standard deviation reported to more significant figures than the actual SD and why don't you interpolate between the two nearest SDs instead of assuming that the SD does not vary with dose?
Answer: With respect to the first part of the question, BMDS currently reports the same number of significant figures in its SD estimates, regardless of the number of significant figures in the data that the user enters. Thus, when interpreting/using BMDS estimates, the user must decide on the number of significant figures to consider. In future versions of BMDS, EPA will strive to appropriately standardize the number of significant figures reported. Giving appropriate consideration to the number of significant figures entered by the user. With respect to the second part of the question, as mentioned in responses to the previous questions, the user can model the variance or assume constant variance (or in the case of lognormality a constant coefficient of variation) across dose groups.

Question 5, Continuous Slide 12: Can we still using relative deviation as the BMR type?
Answer: Yes, relative deviation (from the control mean) is one of the options for BMR Type for the BMDS continuous models (see slide 13).

Question 6, Continuous Slide 13: Can we use one standard deviation as the BMR?
Answer: Yes, you can enter any value for the BMR factor (BMRF) to multiple the control SD by any factor to create the BMR you want.

Question 7, Continuous Slide 9: Jeff It would seem more statistically valid to verify the shape of the distribution of the response instead of assuming a normal distribution by default. Is there a method in BMDS that would allow for selection of an alternate distribution as a basis for the BMR?
Answer: There are methods/tools available elsewhere to assist in making this determination. BMDS has not incorporated such tools as yet (other than to allow users to use both assumptions and compare the results).

Question 8, Continuous Slide 11: Doesn't your assumption that the SD of the control group is the same as for the exposed groups assume that the mode of action for the endpoint for background occurrence is the same as that for that caused by exposure to the chemical?
Answer: The variance models in BMDS at this time do not model controls separate from exposed groups. However, the possibility that the mode of action for the endpoint for background occurrence is the same as that for that caused by exposure receives support when a constant variance model adequately describes the relationship between variance and dose. Conversely, this possibility is not supported when a non-constant variance model (e.g., the BMDS model that estimates variance as a power function of the mean) adequately describes the relationship between variance and dose.

Question 9, Continuous Slide 8: 'In the absence of any other idea of what level of response to consider adverse, a change in the mean equal to one control standard deviation from the control mean can be used', is this true when variances vary among dose groups but data are normally distributed?
Answer: In general, yes, as long as you are able to adequately model the variance across dose groups using the power model that BMDS uses for the continuous models.

Question 10, Continuous Slide 14: if we use the hybrid approach as our BMR type can we then apply log normality to our data and thus use other continuous models instead of just exponential only?
Answer: The Hybrid approach is not available in BMDS at this time. EPA plans to implement the hybrid approach soon. However, when the hybrid approach is implemented, the distribution assumption (normality or lognormality) becomes more important since the tails of the estimated distributions are used to derive the BMD rather than the means. Thus, EPA plans on expanding the lognormality option to all of the BMDS continuous models before implementing the hybrid approach.

Question 11: How does the background probability specified in the model relate to the spontaneous incidence of effects in your control group? I'm thinking of some strains of animals that have high incidence say of certain tumors, which might increase with exposure to test chemical? Is this already taken care of if you have effect > 0 animals in control group? Thanks
Answer: Tumor incidence would represent a dichotomous endpoint. So, I'm not sure how this question fits into the current discussion of continuous response measures. In general, however, background probability is not specified, but estimated by the BMDS dichotomous models. The Extra risk BMR used in the dichotomous models takes into account the estimated background rate. The BMDL estimation also takes into account the estimated background rate (high background rate essentially reduces sample size).

Question 12, Continuous Slide 34: What option do we have if the results indicate that variance is NOT homogenous, so we ran with non-homogenous variance option, but then the result for test 3 says that the modeled variance may not be adequate?
Answer: Your options you have at this point are limited. Since we have no other variance models built into BMDS, you could try a different dose metric or assess another endpoint.

Question 13: What is the recommended BMR if the continuous variation is observed in a pre-condition and we don't know the actual rate of the precondition ending up in a disease? Consider 2 scenarios: 1) the precondition is present in the controls but is aggravated by toxin exposure. (2) Pre-condition is not in the controls but is dose dependent in the exposure groups. The pre-condition is very likely to develop in[to] the disease of interest but we don't have data on how many animals with this pre-condition will end up getting the disease.
Answer: It seems you are talking here about a pre-condition (or precursor event) that can be caused by exposure, but can also exist pre-exposure (from other causes) and be aggravated by exposure. Our response to this question will vary depending on the specific pre-condition and associated disease in question. Thus, we cannot suggest an approach or a BMR that that will be appropriate for all scenarios. If there is no information about the rate at which the pre-condition leads to the disease of interest, one cannot predict the disease rate from the pre-condition. However, a benchmark dose analysis of the precondition might still be useful. For instance, if the pre-condition is a key step in a non-linear mode-of-action leading to disease, it might be possible to estimate a dose that would not be expected to increase the risk of disease by estimating the dose that would not be expected to cause (or exacerbate) the pre-condition. The choice of BMR for the pre-condition would depend on a number of factors related to both the quality of the data and the severity of the pre-condition. If the pre-condition is considered to be an adverse effect in and of itself and/or the likelihood of its progression to a disease state is considered to be high, the choice of a BMR might not be any different from the choice of a BMR for the derivation of a reference dose, i.e., the BMR should result in a BMDL point of departure (POD) that is proximate to the observed data and, after accounting for uncertainty and variability via uncertainty factors or other (e.g., probabilistic) methods, represents a dose that would not be expected to cause an appreciable increase in the risk of experiencing the pre-condition, even in subpopulation that are sensitive to (or are already experiencing from other causal factors) the pre-condition. However, if the pre-condition is not itself adverse and/or the likelihood of its progression to a disease state is considered to be low a higher BMR might be justifiable.

Follow up: What about the case where [the BMD analysis is performed on laboratory animal data] and only the pre-condition is seen in the animals and they never go on to a full blown disease as in humans. An example is atherosclerotic lesions in mice, and coronary heart disease in humans. Wasn't it mentioned yesterday that the recommended BMR for a pre-condition should be 20% for dichotomous data? What would be the equivalent BMR for such data in continuous modeling: SD of 2.0?
Answer: Whether the precondition measured in test animals is relevant to humans would depend on what is known about the mode of action, particularly the steps leading to the development of the precursor lesion. If those early steps are the same in rats and humans, the precursor lesion might be a relevant endpoint regardless of whether it progresses further in the test animal. In discussion the BMR for dichotomous effects, we indicated that a higher BMR (e.g., 20%) might be justifiable for pre-cursor effects. As indicated above, the choice of a BMR for a pre-condition (or precursor effect) would depend on a number of factors related to both the quality of the data and the severity of the pre-condition (or precursor effect). Thus, the BMR for dichotomous or continuous measure of a precondition would have to be determined on a case-by-case basis.

Question 14, Continuous Slide 36: So when the test 2 p value is < 0.1 then we have to uncheck the constant variance box in the option file, correct?
Answer: In general, yes (though we should note that the 0.1 criteria is an EPA recommendation and others have used less stringent criteria such as 0.05).

Question 15: Does the BMDS indicate what the corrected BMR should be for the reduced number of samples, e.g., if 10% is good for the standard cancer bioassay and the high background reduces the sample size, shouldn't the BMR be changed?
Answer: Yes, BMDS accounts for this situation is Extra Risk is chosen as the risk type for dichotomous data. Extra Risk (EPA standard) accounts for background rate (i.e., the 10% for Extra Risk is 10% of the total animals after subtracting background).

Question 16, Continuous Slide 41: So at a glance [for the] the best way to judge if the model is a good fit do we check the p value in the description or the descriptive statements telling us if the modeled variance appears to be appropriate?
Answer: The text associated with the fit tests is provided to help you interpret the p-value. If you agree with EPA's use of a 0.1 criteria then you can generally follow the text, but if you want to use another criteria (e.g., 0.05) you can pay more attention to the p-value.

Question 17, Continuous Slide 42: Since the Hill model is symmetrical around the ED50 data, isn't the high dose "reflective" of the equivalent low dose and therefore informative of the low dose part of the dose-response curve and therefore should not be dropped?
Answer: You would have to have a lot of faith that the Hill model is the true model to take this approach. In general, I don't think we'd say that this feature of the Hill model has a strong biological basis.

Follow up: Interesting response, since the Hill model was derived independently for enzymes, viruses, and cellular receptors and, if I remember correctly, only assumes steady state, mass balance, and the "receptor" is in excess with regard to the "ligand". My assumption for dropping a high dose would be the assumption that the rate-limiting step of the MOA has changed, but I don't know how to justify that based on BMDS decision criteria.
Answer: In general, unless there is substantial evidence that suggests that the high dose response is not as relevant, the preference would be to model all of the response data if possible. An alternative to the Hill model for receptor mediated responses might be the complex exponential model.

Question 18: is the BMDS 2.5 compatible with Mac?
Answer: No, unless you partition your Mac and install Windows operating system in one of the partitions.

Question 19: BTW, you may remember that in enzymology there are a lot of variations on the Hill model, e.g., for receptors that have sites for multiple copies of the ligand such as the 4 binding sites for oxygen in hemoglobin, for which the affinity changes depending on the number of ligands already bound, that might be interesting for consideration for addition to BMDS. Those might be another solution to this issue.
Answer: Good point. If suggestions like this are submitted via e-mail (gift.jeff@epa.gov) we can run them past the EPA BMDS steering committee.

Question 20, Continuous Slide 52: All scaled residuals are outside the absolute value of 2 except the high dose group. Does this mean the data should not be modeled or just not using the power model?
Answer: Scaled residuals are model dependent, so bad scaled residuals for the power model do not necessarily mean the data cannot be fit with another model.

Question 21, Continuous Slide 60: If you had continuous BMD results where one model gives a P for fit of 0.8068 and the next closest is 0.44, however the higher P value has a higher AIC of -59.66 vs. -60.06. Which is best?
Answer: The EPA method (described in more detail in EPA, 2012 BMD Guidance) would indicate that p-value is only used to judge a given models fit to the data. AIC is used to choose between models. Thus, you might choose the model with the lower p-value in this case (presumably because it is a simpler model; uses less parameters to get a similar adequate fit).

Question 22, Continuous Slide 90: Everytime you run the BMDS or wizard software it generates a series of files (.out, .plt, .emf), do we have to keep these?
Answer: These are output files. They will get overwritten every time you rerun the same Wizard or BMDS run. In general, you should keep them, but the advantage of the Wizard is that it holds all of your options and data in one file, allowing you to recreate your output at any time as long as you don't change any of the data or options in the Wizard file.

Question 23: From a security perspective, what did the presenter just say what NOT to do with file save structures and locations? This should be shared with all of us upfront if it "derails" systems - thank you.
Answer: Nothing you do in BMDS or Wizard should impact your operating system or other programs you are running or network negatively. However, certain installation locations may negatively impact how BMDS runs. It is recommended that you place the BMDS folder (and its subfolders) in the simplest (shortest without special characters or spaces) directory for which you have administrative rights (Note: for most EPA users, this will be C:\User\[EPA user's LAN ID]; for non-EPA users, this could be as simple as C:\).

Question 24: I will often be modeling acetylcholinesterase data, so I know I have to use the Exponential model. Can I delete all of the non-exponential model columns from the wizard and save as a new 'exponential' only wizard?
Answer: Yes, that is a good idea.

Question 25: To remove the polynom models #4 and #5, do you just select those rows and delete?
Answer: No, just delete the cells associated with those models (not the whole column or row).

Question 26: The wizard does not perform calculations; the following message is given: "Commas are not recognized by BMDS..." --> but there are no commas introduced in the data and I already reentered the data - any tips?
Answer: Make sure there are no commas or other such symbols in any file or directory names associated with your BMDS or Wizard runs.

Question 27: After checking if P-values for all tests 2, 3, 4 is >0.1, do we visually examine the graphs or just move on to check how BMDLS are spread out?
Answer: Look at scaled residuals to make sure they are not too big, then examine visual fit, then look at BMDLs.