Session 1 – Introduction and Modeling Dichotomous Data – Questions and Answers

Question 1, Intro Slide 1: BMDS will start but there is an error when I try to run a session
Answer: If you have installed BMDS and are having any technical difficulties, make sure BMDS is installed in a directory for which you have read/write permission and also be sure the directory names do not contain special characters such as periods or commas. (Note: see the "Troubleshooting" section of the BMDS Help manual/file for additional details, including special characters to avoid)

Question 2, Intro Slide 1: I made sure I have read write permission - says file 10cancer.exe does not exist, however the file is in the same subdirectory as BMDS250.exe. The path is: "\\vmware-host\Shared Folders\Documents\My Documents\RiskDocuments\BMDS\BMDS250"
Answer: It looks like you have BMDS installed in a network directory. Can you install it to your local computer (e.g., the C: drive) or other root directory where you have read/write permission?

Question 3, Intro Slide 1: I am running on an apple computer with windows 7 installed in a VM ware program. I moved to my documents and it is now working, Thanks
Answer: Great!

Question 4, Intro Slide 1: I seem to be haveing the same problem - the error message says that I have an illegal character [(,)] in my directory or file name even when I completely change the file name.
My path is PC>Windows8_OS (C:)>Program Files>BMDS250_20140522(1)
Answer: It looks like you have not "unzipped" the BMDS250 folder to your computer. If you have read/write permission, unzip the BMDS250 folder, with subfolders, to your C:\ directory.

Question 5, Intro Slide 9: FEL definition?
Answer: Frank Effect Level

Question 6, Intro Slide 16: If there exist only one study that has proper dose response established along with NOAEL identified can we use this data to derive a BMD/BMDL
Answer: Yes, BMD and BMDL derivations are generally done from a single study, though there are exceptions (e.g., use of categorical regression; CatReg), but this depends on the quality of the study and whether "data are worth" modeling as Allen is discussing now.

Question 7, Intro Slide 16: For dichotomous data if BMR of 1% is more conservative, what is the comparable more conservative BMR for continuous? Is it 0.1?
Answer: This depends on the endpoint being evaluated and the type of BMR being used. If using a relative change in the mean response vs control, then 5% would be more conservative than a 10% change that is often used (e.g., for changes in body weight). If using a BMR based on a SD shift in the control mean, a 0.5 SD shift would be more protective than a 1 SD shift that is often used as a "standard" continuous response BMR. The continuous response module (Session 2A) contains a more detailed discussion of BMRs for continuous response data.

Question 8, Intro Slide 16: Another good example of when EPA has used a BMR lower than 10% is the 1% that was used for TCE and fetal heart defects.
Answer: Yes, good example.

Question 9, Intro Slide 16: Please tell me if I am interpreting this correctly - if the BMDL10 represents the dose associated with a 10% response, it is true that there will always be some portion of the population responding, even if you drop to a BMDL1 (1% response)?
Answer: The risk at the point of departure (NOAEL or BMDL) will generally not be zero. This is why we use uncertainty factors. In the future EPA is moving towards estimating a risk probability (with confidence bounds) at multiple dose levels in tis assessments. The topic of BMRs for dichotomous endpoints is discussed in greater detail in the dichotomous modeling module, later in Session 1.

Question 10, Intro Slide 20: if the data are available only through research article (not complete study detail), is it still possible to derive BMD.
Answer: Generally, yes, but it is sometimes necessary to contact the primary author for details of the study that can give more confidence and support to the BMDL derivation.

Question 11, Intro Slide 25: What study design recommendations could you provide to proactively design a study so that the chosen dose levels will allow for BMD modeling?
Answer: There is a paper by Kan Shao from a couple years ago (Shao and Small, 2012) that addresses this. Generally speaking the more dose groups the better for BMD/BMDL derivation. This is true even when holding the number of animals on study steady.

Question 12, Intro Slide 25: Just a thought: On the one hand NGOs press not to use/reduce use of animals for experimental purpose. Given this it is difficult to have large sample size. On the other hand, study quality is better with large sample size and the interpretations are accurate.
Answer: Yes, holding the number of dose groups steady and reducing the number of animals on study will generally reduce confidence in a BMD analysis. However, as Shao and Small (2012) have reported, a change in study design such as increasing the number of dose groups can increase confidence in a BMD analysis without increasing the number of animals used.

Question 13, Intro Slide 26: When we did that we got a d-r curve (not from BMDS) similar to the one on lower-right hand side of slide#26 – what's your opinion on that?
Answer: I would be skeptical of the DR on the lower right hand side. The very steep increase in response over such a small range of doses is a concern.
If there were additional doses between 0 and 150 that matched well with that curve, then that concern might be alleviated. A dose between 0 and 50 would be particularly helpful to inform the low dose region the way the dose at 50 anchors the low dose region in the first slide (top left).

Question 14: This is a follow-up to my earlier question: Thanks for pointing out that 0.5 SD or 5% BMR would be more conservative. But if we would like to find an extremely conservative estimate wouldn't 1% and 0.1 SD be the choice for dichotomous and continuous respectively?
Answer: Maybe, but at that low of a BMR you'd probably be way below the observable range of the data, which could impart considerable model uncertainty.

Question 15: At some point during the seminars this week, can you explain the concept of HEC99 (or HED99) in combination with the BMDL01 (or 05 or 10) (e.g., TCE POD is HEC99BMDL01). This becomes a very difficult concept to explain (and understand), in part because it combines the concept of the 99th concentration and the concept of a 1% response.
Answer: In the TCE assessment (EPA, 2011), a physiologically based pharmacokinetic (PBPK) model was used to convert external rodent exposures/doses to toxicologically relevant internal dose metrics. Where possible and appropriate, the relationship between these internal dose metrics and rodent

noncancer study responses was evaluated using a BMD approach to derive a BMDL-based internal dose point of departure (idPOD). Most responses were evaluated for a benchmark response (BMR) of 10% or 5%, but some more severe responses such as fetal heart malformations (Johnson et al., 2003) were evaluated at a BMR of 1%, resulting in an idPOD = $BMDL_{01}$ in units of internal dose for this effect. A human PBPK model was then used to derive a human equivalent concentration (HEC) or dose (HED) from the idPOD. In the case of TCE, a Bayesian analysis of the TCE PBPK model was used to characterize the uncertainty and variability in the PBPK model-based HEC and HED derivations (for details of how the analysis was done see Section 5.4.1.2 of the EPA 2011 TCE assessment). From this analysis, HEC_{99} and HED_{99} values were derived which can be interpreted as the 99th percentile of the combined human uncertainty and variability distribution of continuous human exposure concentrations that lead an internal dose equal to lower confidence limit of the rodent internal dose at a BMR of 1% (i.e., the idPOD = $BMDL_{01}$).

Lacking information to inform uncertainty and variability, the human equivalent POD is normally divided by interspecies (UF_A), human variability (UF_H) and other relevant uncertainty factors (UFs) to obtain candidate RfC and RfD values. Because the PBPK modeling approach used addresses toxicokinetic differences between species, the UF_A is reduced from 10 to 3, with the remaining 3 accounting for toxicodynamic differences between species. Because the HEC_{99} and HED_{99} values address toxicokinetic uncertainty and variability among humans, their use in lieu of the HEC and HED allows for a reduction of the UF_H from 10 to 3, with the remaining 3 accounting for toxicodynamic differences among humans.

Question 16, Dichotomous Slide 12: What do the beta coefficients represent?
Answer: The different Beta coefficients in the Multistage model are factors that the dose is multiplied by for each "stage" or order of the model.

Question 17, Dichotomous Slide 15: Is BMDS able to handle hormetic effects?
Answer: Only the unrestricted Multistage and the unrestricted continuous polynomial models can take on a form consistent with hormesis.

Question 18: Does the program only use AIC? What about Schwarz's criterion? Please elaborate why or why not, thanks.
Answer: At this time, BMDS models report AIC values for use in comparing model fits, while rewarding parsimony. The Schwartz criterion makes use of the Bayes Information Criteria (BIC). The BIC is currently not reported by BMDS models, but EPA is considering the use of BIC for model weighting associated with model averaging approaches under investigation. EPA will also consider adding the BIC to BMDS model outputs. BIC, more than AIC, tends to favor the simpler model, since it has a larger penalty per parameter added.

Question 19, Dichotomous Slide 19: How do you define background?
Answer: This depends on the model. For most models in BMDS, background is the level of response when dose is zero. However, there are some "Alternative" models in BMDS, where background is treated as a "background dose."

Question 20, Dichotomous Slide 22: Why not use r-squared rather than p for overall goodness-of-fit?
Answered: The p-value is preferred because it takes appropriately accounts for model degrees of freedom.

Question 21, Dichotomous Slide 32: if scaled residual is negative we should discard the model or try different model can you please explain?
Answer: No, what you are looking at with the scaled residuals are absolute differences. It does not matter if it is negative or positive.

Question 22, Dichotomous Slide 32: Does your scaled residual need to equal zero at dose 0?
Answer: No, but as Allen explained, due to the importance of the model fit at zero dose (because this estimate is used to establish the BMR) it can be more important for this estimate to be accurate relative to scaled residuals at high doses.

Question 23, Dichotomous Slide 37: And if there is more than a three-fold difference?
Answer: Three-fold is just a rule of thumb. Depending on the situation (severity of the endpoint and steepness of the response), we might decide that a range > 2-fold represents too much model uncertainty, but we generally believe that the range should never be more than 3-fold.

Question 24, Dichotomous Slide 41: Is selecting a model based on lowest AIC a matter of policy?
Answer: The EPA's use of the lowest AIC criterion needs to be distinguished from an approach seeking to reject poor performing models in favor of adequate ones. Rather, the recommended procedure in the draft BMD Technical Guidance (EPA, 2012) is intended as a practical approach for selecting a model among a set of alternative models that already have been determined to have adequate fits (i.e., $p \geq 0.1$ in a goodness-of-fit test). The use of the AIC for comparing model fits is a scientifically justifiable approach. While the EPA does not provide formal guidance on how many significant figures to consider for this purpose, all else being equal, "any difference" reported by the BMDS models is often used for practical/policy reasons to "break ties" and avoid more subjective "model shopping."

Question 25, Dichotomous Slide 41: Do you recommend using AIC and not AICc (corrected)?
Answer: The AICc has value in that it accounts for sample size, but is not something that is directly estimated by BMDS at this point. It is, however, something EPA may consider for future BMDS modifications.

Question 26, Dichotomous Slide 42: Should you combine BMDLs or should you combine the BMDs and re-estimate the lower bound on the combined central estimate?
Answer: Specific recommendations for "combining" BMDLs are not going to be published by EPA until EPA approves a "model averaging" approach that appropriately weights the modeling for this purpose.

Question 27, Dichotomous Slide 43: If more than one model adequately fits the data, is it appropriate to average the model results?
Answer: At this point, EPA guidelines only recommend combining BMDL results when model AICs are the same (to the number of decimal points deemed by the user to be relevant). EPA is working on developing a model averaging approach (e.g., to help address model uncertainty) that will allow for averaging the results of adequately fitting models that do not have equivalent AICs. However, this is not going to be recommended by EPA until EPA develops or approves a "model averaging" approach that appropriately weights the modeling results for this purpose.

Question 28, Dichotomous Slide 47: is Hill model appropriate only for receptor mediated biological effects?
Answer: No, but it may be that you would choose the Hill model apriori if you are modeling receptor-mediated biological effects.

Question 29, Dichotomous Slide 47: thanks! Follow up: so does that mean that hill model output is also valid to be considered for best fit parameters in biological responses that are not receptor mediated?
Answer: Yes, as there are other reasons, including early mortality, that a response can plateau besides a receptor mediated MOA.

Question 30, Dichotomous Slide 47: Is there a large difference between versions 2.4 and 2.5?
Answer: Here is the text from the BMDS website re: the upgrades in 2.5, "The BMDS Wizard has be upgraded to include a new template that allows users to run the MS_Combo model once all tumors have been run using the cancer template. Additionally, an issue with the cancer slope factor not exporting correctly has been resolved. A number of fixes have also been made to BMDS: (1) the "View Plot" functionality has been improved to make it easier to generate and edit a plot from a previously created .plt file; (2) the multistage, multistage cancer, and MS_Combo models now provide accurate results when non-integer input data are used and beta parameters are specified by the user; and (3) the power model now honors the direction of adversity specified by the user."

Question 31, Dichotomous Slide 83: How many significant figures are appropriate for an AIC calculation? The table reports 6, but I doubt that the data used in the equation could justify that.
Answer: The subject table in the training material reports the AIC to the number of significant figures that are reported in the BMDS model output. EPA is concerned that further restricting the number of significant figures reported by BMDS models would be inappropriate in some circumstances (e.g., where the AIC is to be used as an "intermediate" calculation for model averaging). At this time, EPA does not offer formal guidance regarding how many AIC significant figures to consider. This is left to the user's discretion, which allows the user to make a judgement based on the purpose the AIC will serve.

Question 32, Dichotomous Slide 90: Will AIC or lowest BMDL always drive model choice? In other words, if you had a p value = 0.96 that had a slightly higher AIC than a model with a p-value=0.70 should the higher p-value be chosen?
Answer: An adequately fitting model according to EPA's p-value criteria with a higher AIC might ultimately get chosen if it represents a more biologically feasible curve or if the fit at low dose (near the lowest response level of the data) is considerably better. However, the p-value is not used as the basis for such a decision because the p-value does not reward "parsimony" (a preference for the simpler model) the way the AIC does. Thus, the AIC is preferred over the p-value for comparing across models.

Question 33, Dichotomous Slide 91: You said you had a good scaled residual at the dose group nearest the BMD? Is that different than the scaled residual at the BMR? Can you explain that?
Answer : BMR and BMD are related in that the BMD is the model estimate of the dose associated with a BMR level of response. So when we say "scaled residual for the dose group closest to the BMD" we mean "...closest to the model estimated dose for the BMR."

Question 34, Dichotomous Slide 116: for a certain data set I get errors for weibull and gamma models saying " Weibull (or Gamma) plotter encountered some problem. 002 file input for plotter 10Weibull.exe does not exist. Please check your data or input selection"? How do I correct this?
Answer : This kind of error can occur if you have odd/special characters in you directory path names or files names. A good rule of thumb is to simplify your BMDS related directory names and file names to the extent possible. The BMDS Help file contains more specific guidance for how to name directories and file names for optimal use of BMDS.

Question 35, Dichotomous Slide 117: So the BMD and BMDL can come from the observable portion of a dataset? I ask this because some health assessors think of a BMDL as NOAEL.
Answer : Yes, but a NOAEL can come from an "observable portion" of the dataset as well. For example, a 3/10 response over a control response of 0/10 might be a NOAEL, depending on the p-value used for the pair-wise comparison.

Question 36, Dichotomous Slide 117: Agreed. For years, I caution others against thinking of a BMDL as a NOAEL, which is often just misinterpreted as a no effect level.
Answer : Exactly

Question 37, Dichotomous Slide 117: Will the BMR always be the same no matter which model you run? Or could two models produce BMDs that are closer to different doses on the same data set?
Answer : Because the BMR is dependent on the background response estimated by the model, it can change from model to model. Models can give different estimates of the BMD and it is therefore possible for two models produce BMDs that are closer to different doses used in the study.

Question 38, Dichotomous Slide 117: What about the chi squared?
Answer: Chi-squared is used in deriving the p-value, which is a consideration for whether the model fit is adequate.

Question 39, Dichotomous Slide 117: When do you restrict slope? He did for the log probit but not the multistage.
Answer : The Multistage beta coefficients were restricted in the example he presented. We generally restrict model parameters (refer to USEPA, 2012 BMD Technical Guidance).

Question 40, Dichotomous Slide 117: Can scaled residuals be used to compare the models then?
Answer : Yes, scaled residuals are an indication of fit at a given dose group and have been used to exclude models form consideration, and also as a basis for choosing one model over another.

Question 41, Dichotomous Slide 117: So when comparing scaled residuals across models, you could be comparing scaled residuals from different doses, depending on the BMD of the model, correct?
Answer : Unless the BMD estimates are very different across models, you're usually going to be looking at the how well the model fits at the same dataset dose group. However, on rare occasions two models can give BMDs that are closest to different dose groups.

Question 42, Dichotomous Slide 117: I got error message output directory not specified where I have to specified output directory
Answer: You need to specify your output directory (e.g., ...BMDS250\Wizard\Data)

Question 43, Dichotomous Slide 117: What does the error for Multistage 5 signify?
Answer: There are too many parameters in model to evaluate the data.

Question 44, Dichotomous Slide 117: At the end of the day, which value do you pick? The lowest BMDL or do BMDL from the model with lowest AIC?
Answer: We would use the Weibull model result in this case.

Question 45, Dichotomous Slide 117: is a 10% BMR the EPA standard?
Question 46, Dichotomous Slide 117: Is the selection of the benchmark response level (eg. 1%, 5%) based on a statistical or biological determination, or is it EPA science policy?
Answer: There are many factors that go into setting a BMR for dichotomous endpoints. Section 2.2 of the EPA 2012 BMD Technical Guidance Document contains a more complete discussion of benchmark response levels. Section 2.2.1 contains the following summary.

- An extra risk of 10% is recommended as a standard reporting level for quantal data, for the purposes of making comparisons across chemicals or endpoints. The 10% response level has customarily been used for comparisons because it is at or near the limit of sensitivity in most cancer bioassays and in noncancer bioassays of comparable size. Note that this level is not a default BMR for developing PODs or for other purposes.
- Biological considerations may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a BMR greater than 10% (e.g., for early precursor effects) as the basis of a POD for a reference value.
- Sometimes, a BMR lower than 10% (based on biological considerations), falls within the observable range. From a statistical standpoint, most reproductive and developmental studies with nested study designs easily support a BMR of 5%. Similarly, a BMR of 1% has typically been used for quantal human data from epidemiology studies. In other cases, if one models below the observable range, one needs to be mindful that the degree of uncertainty in the estimates increases. In such cases, the BMD and BMDL can be compared for excessive divergence. In addition, model uncertainty increases below the range of data.

Question 47, Dichotomous Slide 117: Could you comment on how to handle wide dose spacing when applying BMD method? It is not unusual to have, e.g., the lowest and mid dose differed by a factor of 10 or more in some in vivo studies.
Question 48, Dichotomous Slide 117: with regard to wide-dose spacing- - please discuss log transforming dose data
Answer: With the advent of dose-response modeling approaches, such as the BMD approach, toxicological study designs have changed in order to better define the shape of the dose-response curve at the low end of the dose-response curve. If the dose groups differ by a factor of 10, characterization of the low end dose-response may be difficult. That difficulty is not overcome by log transforming the doses. Thus, BMDs and BMDLs are generally derived from untransformed doses. However, doses are sometimes log transformed for plotting purposes to help with visualizing the data.

Question 49, Dichotomous Slide 117: Can I use PBPK model derived tissue data instead of external exposure data
Answer: If a PBPK model or other method of converting external doses to internal doses (e.g., target tissue doses) exists and EPA PBPK WG recommends doing the BMD analysis on internal doses, particularly when the relationship between internal and external doses is nonlinear. The internal dose BMDL would then be converted to an external human equivalent BMDL.

Question 50, Dichotomous Slide 117: can the parameter bounds be modified to prevent the AIC penalization?
Answer: Users can modify the lower bound on the power parameter for the dichotomous Weibull model. Otherwise, parameters can either be restricted or not restricted at preset boundaries.

Question 51, Dichotomous Slide 117: If this were cancer data, would the log-probit model have been run?
Answer: In general, EPA's policy is to use the Multistage model for cancer data unless it does not afford an adequate fit or unless there is convincing evidence for a nonlinear mode of action.