Session 3A – Cancer Modeling – Questions and Answers

Question 1: [You should] mention that the 2005 cancer guidelines allow for nonlinear extrapolation from a point of departure (POD) for cancer data.
Answer: Yes, nonlinear extrapolation (e.g., dividing the POD by uncertainty factors) can be used if sufficient mode of action information is available to justify that approach, and the EPA (2005) cancer guidelines describe the information and criteria that is need to make that determination. The EPA Chloroform and EGBE assessments are examples where this approach has been used in IRIS assessments.

Question 2: Is it possible to choose the Hill model if the cancer operates by a receptor mediated MOA such as estrogen?
Answer: Yes, the Hill model (or a margin of exposure type approach) may be justified in some cases, depending on what is known (and how confident we are) about the mode of action. However, EPA's standard approach is the Multistage model when MOA information is either not available or does not suggest that another model would be more appropriate.

Question 3: If the coefficient of the linear term [of the Multistage model] is zero [i.e., during model optimization the linear term is estimated at the zero boundary], does that mean that the MOA should be considered nonlinear? I know the guidelines talk about MOA, but if the model doesn't have a linear term, the usual argument for linearity for low doses, i.e., that the linear term predominates at low doses, wouldn't appear to be accurate.
Answer: The linear term being estimated at 0 is one piece of information that might support the use of a nonlinear assessment approach, but additional biological justification would generally be necessary to support departure from the Multistage model or the application of a margin of exposure type approach (as outlined in the EPA 2005 cancer guidelines).

Question 4: Can cancer mortality data [differential mortality based on dose] be accommodated by BMDS?
Answer: With respect to accounting for early mortality in a cancer bioassay, there are two approaches we will review later in the session, use of the EPA time to tumor, multistage weibull (MSW) model and use of poly3 adjusted (for early mortality) incidence data in the BMDS Multistage and multitumor (MS_Combo) model. One of the improvements made in BMDS 2.5 is to the way the Multistage and MS_Combo models treat fractional incidence data (e.g., incidence data adjusted for early mortality such as poly3 adjustments that can be estimated and often reported by NTP and others).

Question 5: Comparison of Dose Response Curves and BMDs in studies of cancer progression/development will vary between choice of animal model and strains of the same model (e.g., less or more sensitive rat models to a suspected carcinogen). What is the panel's recommendation for comparing dose response curves and BMDs within strains of the same species and between animal model species? Could a ratiometric be used of BMD to estimate relative sensitivity between species or even between suspected carcinogens?
Answer: The answer is largely yes. BMD values can be used for comparative purposes across species as long as other factors (e.g., experimental conditions and study design] not related to species differences are held equal. For this purpose, you might want to use a BMR that is higher (e.g., proximate to the center of the response region) as it would not be as important to be at the low end of the response curve and the midpoint of the curve gives more reliable BMDs for comparison purposes.

Question 6, Slide 16: [For determining what degree of the Multistage-cancer model to use when modeling cancer data,] could you explain the "hitting the bound" part again? If the multistage 3 hit a bound, should we still be considering it?

Answer: At this time, the EPA suggested approach for the situation where a parameter in the model "hits a bound" differs for the application of the Multistage cancer model to cancer data versus all other situations and models in BMDS, including the application of the BMDS Multistage model to non-cancer data. The estimated parameters in the BMDS Multistage and Multistage cancer models are bounded to be non-zero. As explained in Slide 16 and in more detail in an EPA/NCEA Statistical Workgroup (SWG) report available from the BMDS website, for the Multistage cancer model, after fitting all orders (degrees) of the multistage model up to two less than the number of dose groups (step 2 of slide 16), 3rd order (degree) or higher models are excluded from consideration if any of the parameters of any of the models hit the zero bound without actually being estimated (step 3 of slide 16). Further, in this situation, if an adequate fit is achieved by the remaining 1st and 2nd order (degree) models and any of the parameters in either model hits the zero bound (step 5 of slide 16) EPA suggests use of the model with the lower, more health protective BMDL.

For all other BMDS models and situations, including when parameters in the Multistage cancer model do not hit a bound, the normal procedure of examining the BMDLs and AICs from all adequately fitting models, regardless of whether any parameters hit a bound, is suggested (see section 2.3.9, steps 4 and 5, of the EPA BMD 2012 technical guidance).

Question 7, Slide 16: Does this [Multistage-cancer model method described above for considering parameters that hit the zero boundary] apply for the beta0 or background parameter?

Answer: Yes, the approach described above for excluding 3rd order or higher models applies when any parameter, including the background (beta0) parameter, hits the zero boundary without actually being estimated. Even though a negative background parameter estimate is not biologically tenable, it is not actually estimated to be zero by the model when it hits the zero boundary.

Question 8 Slide 16: Would you reiterate when you go to the lowest BMDL instead of the lowest AIC?

Answer: As indicated above, for all models and situations not involving parameters in the Multistage cancer model hitting a bound, EPA recommends the procedure for examining the BMDLs and AICs described in section 2.3.9, steps 4 and 5, of the EPA BMD 2012 technical guidance, which prescribe using the adequately fitting model with the lowest AIC if the range of BMDLs is not too wide (e.g., < 3-fold) and the adequately fitting model with the lowest BMDL if the range of BMDLs is too wide (e.g., > 3-fold). As explained above, when parameters in adequately fitting 1st and 2nd order (degree) Multistage cancer models hit a bound, EPA suggests use of the model with the lower, more health protective BMDL.

Question 9, Slide 34: Once I hit autorun [using the BMDS Wizard Excel program], my file auto saves and them provides results that are all error messages.

Answer: If you are getting "error" results, the problem is likely related to the output directory you have identified on your Main page. Make sure it is one that meets the criteria we talked about earlier for not using special characters (and keeping the directory length short and simple)

Question 10, Slide 42: So for multistage cancer model, we will always use the cut-off p-value of 0.05 instead of 0.1?

Answer: Yes, that is the EPA practice when the Multistage model is used.

Question 11, Slide 44: The select folder function does not work, how can I proceed?
Answer: Make sure you have macros enabled in the excel workbook.

Question 12, Slide 44: There is an error message, macro possibly not available.
Answer: You'll need to go to the trust center in excel and enable the macros so the vba code can run.

Question 13, Slide 49: should I combine male and female tumor data in the same bioassay?
Answer: EPA generally evaluates males and females separately. There are exceptions when gender differences are ruled out and there is a need for more statistical power (greater n) in the dose-response analysis.

Question 14, Slide 50: Is the MS Combo being used to set IRIS values? I recall TCE being associated with multiple cancers but I don't remember if a combo evaluation was done.
Answer: In general, multiple cancers within the same bioassay should be evaluated via the MS Combo model or a similar procedure that appropriately accounts for combined risk from multiple, independent tumor types. The TCE assessment was conducted before MS Combo model was available, but the cancer potency for combined tumor types was estimated in the TCE assessment (see Appnedix G) using comparable methods that involve the use of WinBUGS software (Spiegelhalter et al., 2003) and the application of Markov chain Monte Carlo computations.

Question 15, Slide 63: My combo file says no errors when I press (c) run in BMDS; but when I press (D) it says that the .out file is not found...
Answer: What do you have identified for your output directory?
Response: C:\BMDS250\BMDS250\Data\AFJ-webinar 3B example excel files\
Answer: Simplify and shorten the directory name (e.g., just call it AFJ; the problem could be the name length)

Question 16, Slide 91: In the survival spreadsheet, what is meant by column M "weight"?
Answer: This is the statistically adjusted "weighted" results for the animals (not how much the animal weighs). In the excel file shown in the presentation, there is a "tumor" and a "time-adj" column. The time-adj is (#days an animal lived/# days of exposure)^3. In the tumor column, if an animal has a tumor, it got a value of 1, if not a value of 0. The weight column then has an if/then statement, so that if an animal's tumor value is 1, the weight column equals 1. If not, the weight column = the time-adj column.

Question 17, Slide 100: For an individual tumor site, a BMD_{10} means 10% of exposed have tumors. In the combo it would be possible for one animal to have more than one tumor. How should we interpret the BMD_{10} for the combo model?
Answer: A BMD_{10} from the MS combo model is the estimate of the dose associated with a 10% probability of getting Tumor A or Tumor B or Tumor C.

Question 18, Slide 100: Are there plans to validate BMD applications between laboratories? For example, same rat model, same test compound, same experimental conditions, but perhaps different BMD metric outcomes? How can the technology be compared between groups and centers to secure confidence in comparative analysis between various research groups moving forward?
Answer: This is a good question. I'm not aware of EPA plans to do this, though a recent EPA postdoc that is now at the University of Indiana, Dr. Kan Shao (kshao@indiana.edu), has published research on what is the best study design for BMD analysis.

Question 19, Slide 100: Any plans to make MSW more user friendly and part of BMDS?
Answer: Not currently. The EPA's statistical workgroup (SWG) is investigating the MSW approach versus the use of poly3 adjustments. Preliminary indications are that the poly-3 adjustment adequately addresses concerns regarding differential mortality, and has other advantages in that it is easier to perform and can be used in an MS Combo analysis.