2/17/2012
Sheppard's summary of Group 2 thoughts regarding summary recommendations:

Exposure metrics:

- Priorities as an alternative to current cumulative exposure metric:
    - RTW – residence time weighting
    - Exclude exposure after 1980 (end of Libby processing), enabling exposure-response modeling without lags.
- Other exposure metric options **if there is time**:
    - Other weighting schemes:
        - More heavily weighted to early life than RTW
        - Clearance time weighting
    - Mean exposure
    - Combine other metrics with post Libby processing exclusion (exclude exposure after 1980)
    - Double exposure for measured PCM data to accommodate modern PCM (make consistent with today's technology)
    - If any such information is available, use industrial hygiene data prior to 1972 from other expansion/exfoliation plants to find alternative "measures" for basing the reconstruction
    - Because of biological reasons and features of the dataset, consideration of lagged exposures is still important and should be incorporated in the assessment of exposure metrics to some degree. (Note: This only applies for exposure metrics that include the post 1980 time period. A reason for excluding exposure after 1980 is so exposure-response modeling can be done without lags.)

Suggestions for fine-tuning the RfC estimate:

- Investigate alternative exposure metrics. We identify two primary exposure metrics (in addition to cumulative exposure) and encourage additional metrics be reviewed in sensitivity analyses as time permits. Consider these alternative exposure metrics along with alternative functional forms for the dose-response. (i.e. don't restrict this assessment to the Michaelis-Mentin model, particularly if the fixed plateau is adopted)
- For the RfC, divide by 70 regardless of exposure metric (justification: with prevalence data, lagging should not be connected scientifically to a lifetime since we don't know the timing of the event. From this perspective all exposure metrics are just alternative measures and don't necessarily reflect appropriate lifetime duration.)
- Conduct analyses fixing the plateau at e.g. 85% or other value justified from the literature. [Possible reference: Lilis R, Miller A, Godbold J, et al. Radiographic abnormalities in asbestos insulators: effects of duration from onset of exposure and smoking: relationships of dyspnea with parenchymal and pleural fibrosis. Am J Ind Med 1991; 20:1-15.] Consider the fixed plateau model as a primary approach (rather than sensitivity analysis) since the data

are not sufficiently rich at high exposures to support estimation of the plateau. (Along with fixing the plateau it will be important to estimate the coefficient for exposure, i.e. replace Michaelis-Mentin with Dichotomous-Hill model.)

- When comparing candidate models consider:
    - Model fit in the region of the BMR by comparing the fitted curve with the data, e.g. by plotting using a locally weighted smooth curve (with low enough degrees of freedom to maintain monotone non-decreasing shape).
    - Assess the plausibility of the model (biologically/epidemiologically). Address this in the context of the technical guidance and possibly incorporate these findings into the selection of the primary model.
    - Align the approach with EPA technical guidance document (EPA 2000a; http://www.epa.gov/raf/publications/pdfs/BMD-EXTERNAL_10_13_2000.PDF) where appropriate and justify both following and deviating from the guidance document. In other words, follow the guidance thoughtfully rather than dogmatically.
        - In selecting the BMCL, we encourage deviating from the technical guidance by downweighting the lowest AIC criterion (among models with essentially identical AIC estimates) and upweighting selection of the model providing the lowest BMCL among all models with reasonable fit in the region of the BMR. (For technical guidance details see pages 34-35 of http://www.epa.gov/raf/publications/pdfs/BMD-EXTERNAL_10_13_2000.PDF)
- Uncertainty assessment: Refine the description, merging and/or using insights across the two uncertainty sections

Recommendations for approaches to the full cohort revised analysis to be used to substantiate the RfC estimate:

- Revisit the choices for the dose-response modeling:
    - Consider fixing the plateau rather than estimating it.
    - Base modeling on the Dichotomous-Hill model rather than the Michaelis-Mentin model because this model allows estimation of the exposure slope parameter. When adding additional covariates, changing the exposure metric, and/or fixing the plateau, it will be important to allow the exposure effect to scale in the model based on the best fit of the model.
- Handling TSFE:
    - Drop modeling of the plateau with TSFE in favor of incorporating this term as a covariate in the model (along with consideration of alternative exposure metrics that give more weight to earlier exposures, thus possibly reducing the importance of TSFE). Consider using a fixed plateau based on a literature value.

        - Include TSFE in the "linear predictor" part of the model, much as smoking was considered in sensitivity analyses of the subcohort.
        - Consider the functional form of TSFE by evaluating some arbitrary smooth functions or a polynomial function
- Evaluate the highest priority exposures as identified from the subcohort analysis along with additional exposure metric considerations based on scientific understanding (i.e. a few additional exposures should be explored in the full cohort since the data are richer)
    - See exposure metric priorities
    - Consider some "what if" exposures using different plausible assumptions for the exposures in various areas of the plant during the time period with no area concentration measurements. One suggestion is to take average concentration measurements from other plants processing Libby vermiculite during the time period of interest. (We recognize that this will only be possible if such data exist. Are there some impinger data that can be used?)
- Discuss the fundamental attributes of the models, particularly the selected model
    - Better describe the fitted model with some consideration of epidemiological/biological plausibility
    - Balance competing priorities of consideration of plausibility vs. following the technical guidance
- Keep the database uncertainty factor at 10; don't drop it to 3.
- Other options if there is time:
    - Additional exposure metrics
    - Alternative values for the pre-specified background (.02%, higher values than 1%)

Additional thoughts on substantiating the RfC estimate:

- If resources permit, document and discuss the cause of death of the deceased cohort members to help support the choice of RfC.

Data description

- Enhance the data description to foster trust by providing more background information and more model assessment information.
- Background information: Provide more basic data description of the two Marysville cohorts akin to the kinds of information that appears in the opening descriptive tables of most epidemiological study papers. Enhance this by
    - Including richer information on exposure distributions for all exposure metrics considered (min,max,quartiles,mean).
    - Clarifying details about the various radiographic outcomes.
    - Showing a cross-tabulation of the number of individuals in the quintiles of exposure and TSFE. (Possibly also add number of cases in

addition to number of individuals.) For comparison, most likely show the same tabulation in the subcohort (with quintiles defined in the full cohort).
    - Showing scatterplots to compare different exposure metrics
    - Showing a scatterplot of exposure vs. TSFE in the full cohort (and possibly also in the subcohort if informative).
- Provide richer description of the fitted model(s)
    - Expand the graphical presentations
    - Include rug plots for exposure as appropriate
    - Show stratified groups as appropriate
    - Show raw data as appropriate
    - Include uncertainty estimates as appropriate (e.g. for raw estimates of prevalence in stratified groups where cell sizes may vary considerably).