

Comments by Weihsueh Chiu on the Swartout paper from a “regulatory/risk analyst” point of view.

Disclaimer: These comments are those of the author, and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

This approach is probably the most straight forward “extension” of what is currently standard practice from the current guidelines. It basically proposes two steps:

(1) Comparison of the pooled model and summed individual model deviances to assess whether pooling is statistically justified.

(2) Using a parametric bootstrap to calculate confidence bounds, for comparison with the profile likelihood method.

From a regulatory point of view, these practices would probably be relatively easily justified. In addition, (1) is readily implementable with current software, and (2) does not seem like a substantial additional computational burden. Thus, this seems like a good “baseline approach” with which to compare to the others.

I have six comments/questions:

1. The analysis with different empirical dose-response models seems to affirm the efforts and reasoning of the EPA Cancer Guidelines to make the dose-response analysis (in the range of observation) relatively model-independent. In particular, the empirical models are most robust in the range of observation – as the BMR declines below that range, the uncertainty goes up, particularly with flexible models such as the Weibull. Moreover, statistical tests are poor at distinguishing between models. This is the justification for the separation of dose-response analysis in the range of observation from extrapolation to low doses.
2. Interestingly, the fairly common practice of taking the geometric mean of different slope factors (e.g., males and females for frambozadrine) is clearly does not yield the same results as calculating a slope factor after pooling the data. This is true whether one uses the BMD or BMDL. For the BMDLs, this is not surprising, since you are combining two tail estimates, and would expect the combination to be further out into the tail. However, it is also true with the BMD, which seems important. Thus it matters which “pooling” you do first -- the data or the slope factors. Interestingly, in epidemiological meta-analysis, one often tries to pool as many studies as possible, separating out only if there is heterogeneity (either statistical or due to a strong a priori information)
3. In the frambozadrine and persimonate examples, it was concluded that the studies could be combined. It would be interesting to see visually “how much” deviation is necessary to conclude that study cannot be pooled.
4. In the examples here of combining datasets, the dose-response shapes were similar even by “eyeball.” It is not clear to me how to test for and implement BMD models in which some component of the dose-responses were similar and some were not. As an example, what if the background rates were different, but the additive (or relative) treatment effects were the same. Alternatively, what background rates were the same, but the treatment effects were different.

5. How would this compare with a non-linear mixed effects -- i.e., using tests of heterogeneity to determine whether the treatment effect is fixed or needs additional random component (related to previous comment, perhaps).
6. My final question is more of a technical one, regarding the AIC/Deviance measures. Clearly small differences are of no consequence, but large differences are important. However, how does one determine how "small is small?" Does an "uncertainty analysis" on AIC/deviance need to be performed? How would one do it? While the use of a BMR in the range of the data should minimize the impact of "errors" in model choice due to "variance in the AIC/deviance," if the AIC/deviance is to be used to decide whether to pool or not to pool data, it could have a greater impact. A characterization of the "frequentist" properties of using the test statistic for "to pool or not to pool" may be useful -- i.e., what are the type I and type II error rates?