Dose-Response Modeling and Lifetable Analysis cont.

Table 1 summarizes the data used in the case study of iAs and bladder cancer, including the estimated intake values and effective counts calculated as described in the Poster 6

For the purpose of dose-response modeling, the $a^*$ parameter was assumed to be independent for each dataset.

Methods also assume study-specific $\beta$ values that are normally distributed around a mean of $\beta_{\text{mean}}$, with standard deviation $\beta_{\text{sigma}}$. Both $\beta_{\text{mean}}$ and $\beta_{\text{sigma}}$ were assigned priors and updated (Table 2)

The gamma distribution for $\beta_{\text{mean}}$ reflects determination that iAs is causally associated with the development of bladder cancer.

Prior judgement that exposure to 1 µg/kg-day iAs (~14-fold average background exposure) is highly likely to result in 1.0001 < OR < 20.

1% and 99% percentiles of gamma distribution ($f(x) = \frac{\text{gamma}(x)}{\Gamma(x)} x^{\alpha-1}\exp(-\alpha x)$, set equal to ln(1.0001) and ln(20), results in parameters listed in Table 2.

Importantly, note that gamma distribution gives greatest weight to values of $x$ closest to zero (hence, prior assumption is weaker association with iAs unless data are sufficient to override prior).

Estimates of pooled and study-specific $\beta$ values derived from hierarchical model and estimated lifetime extra risks in the target population are summarized in Tables 3 and 4 and Figures 1-5.

The sensitivity of the hierarchical model and its outputs were examined regarding four sources of uncertainty:

1. Characterization of exposure levels used in the modeling: this was addressed using the "high" and "low" dose estimates discussed in Poster 6; using different estimates of dose did not result in pooled $\beta_{\text{mean}}$ that differed greatly (0.19, 0.20, or 0.21).

2. Choice of datasets: a leave-one-out analysis was performed which showed that no one study had a disproportionately large influence on the final pooled $\beta_{\text{mean}}$ value (Table 5).

3. Zero background inhalation assumption: assuming background inhalation exposures of 0.2 to 0.6 µg/day decreased mean extra risk estimates from 4.08 $\times$ 10^4 µg/kg-day (Table 5, no data set excluded) to 4.68 or 4.51 $\times$ 10^4 µg/kg-day.

4. The consideration of alternative gamma prior distributions for $\beta_{\text{mean}}$: alternative distributions that considered different 1% or 99% percentile values did not overly influence final risk estimates (Table 6).

Conclusions

These Bayesian meta-regression methods (Posters 6 and 7) allow for inclusion of more studies than other meta-regression methods by reconciling different study designs and exposure metrics, and could potentially be applied to any endpoint for which multiple studies and incidence/mortality/morbidity lifetables are available.

The logistic dose-response model used could be extended to consider fractional-polynomial forms of the logistic model, $logit(p(x)) = a^* + \beta_1 x + \beta_2 x^2$, to allow more flexibility in fitting datasets for the investigation of whether the data suggest a J-shaped dose-response (e.g., negative slopes in the low dose region).

References