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Comments on Gradient Report, "Review and Verification of Existing Sulfolane Dose-Response Assessments", dated August 15, 2014.

General Comments

As listed in Table 3.13 in the Gradient Report, the Linear, Power, and Polynomial models generally reverted to the linear form. Hence, this family of models only provided one unique dose-response model.

The Gradient Report provides a comprehensive review of published animal studies that investigate biological effects in animals exposed orally to sulfolane.

Specific Comments

Table 2.2 in the Gradient Report lists the dose-response data used to calculate benchmark doses (BMD's) for various biological effects observed in animals exposed orally to sulfolane. Table 3.13 provides a summary of BMD's calculated.

Gradient implies on page 12 of their Report that U.S. EPA's approach was followed in using the results listed in Table 13.3 to calculate a Point of Departure (PoD). EPA's in its BMDS Wizard indicates that BMD/BMDL ratios exceeding a factor of 5 indicate imprecise estimates of effects and should not be used for determining the PoD. However, Gradient did not follow the EPA's BMDS Wizard approach and used all of the results in Table 3.13 to set a PoD including several results where the BMD/BMDL ratio exceeded 5, e.g., for white blood count with concurrent controls for exponential model 4, BMD/BMDL = 32.96 / 4.75 = 6.94.

Hence, applying the EPA approach for using only results where the BMD/BMDL ratio is less than 5 restricts the results for the white blood count with concurrent controls to the linear model with a BMDL = 12.66 mg/kg-day and the exponential model 2 with a BMDL = 6.99 mg/kg-day. According to the EPA's approach, since these two BMDLs are within a factor of 3 they are considered sufficiently close and the model with the best goodness-of-fit, lowest Akaike Information Criteria (AIC), is selected (in this case the linear model with the BMDL = 12.66). Recall that this model is linear for the transformed dose, ln(dose +1).

For the white blood count with historical controls only the linear model satisfies the criterion of the BMD/BMDL less than 5, giving a BMDL = 16.12 mg/kg-day.

For lymphocytes with concurrent controls only the linear model satisfies the criterion of the BMD/BMDL less than 5, giving a BMDL = 14.45 mg/kg-day.

For lymphocytes with historical controls only the linear model satisfies the criterion of the BMD/BMDL less than 5, giving a BMDL = 15.89 mg/kg-day.

Since these four BMDL's listed above are within a factor of 3, they are not considered divergent (see Section 4, page 12 of the Gradient Report). According to the U.S. EPA BMD Analysis Framework, Figure 3.1, the BMDL selected for the PoD is based on the qualifying model with the lowest AIC. For the four qualifying BMDL estimates listed above, the linear model with concurrent controls for lymphocytes with a BMDL=14.45 mg/kg-day has the lowest AIC (see Table 3.13). Hence, the **recommended PoD= 14.45 mg/kg-day,** as opposed to the PoD = 6mg/kg-day suggested in the Gradient Report which failed to disregard imprecise results where the BMD/BMDL exceeded a factor of 5.