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MEMO

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| To:  Toxicology Excellence in Risk Assessment  Sulfolane Peer Review Meeting | Copies: |
| From: |  |
| Brian Magee, Ph.D. Vice President, Principal Toxicologist |  |
| Date: |  |
| September 8, 2014 |  |
| Subject: |  |
| Response to Comments Made in Gradient’s Review and Verification of Existing Sulfolane Dose-Response Assessments | |
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This memorandum responds to comments made in *Review and Verification of Existing Sulfolane Dose-Response Assessments* (2014), prepared by Gradient Corporation (Gradient) for the Alaska Department of Environmental Conservation (ADEC), in regards to ARCADIS’ derivation of an oral reference dose for sulfolane. The information in this memorandum clarifies activities performed by ARCADIS (Magee, 2012) during its independent derivation of an oral reference dose (RfDO) for sulfolane in support of developing a groundwater cleanup level included in the 2012 Revised Draft Human Health Risk Assessment (HHRA) (copy attached) for the North Pole Refinery, North Pole, Alaska.

**COMMENT 1**: In reference to Magee (2012), Gradient (2014) states on page 5 that:

“*ARCADIS did not report any alternative BMD analyses, rather provided only a critique of existing analyses*.”

**RESPONSE 1**: ARCADIS’ study of the human health impacts of sulfolane related to the North Pole Refinery Site is described in the 2012 Revised Draft HHRA in which it independently identified primary toxicology studies with relevant data, evaluated the strength of each data set, and performed Benchmark DoseLow (BMDL) analyses using the biological effects data reported in the Huntingdon Life Sciences (2001) study and adhering to EPA guidance (1995, 2000, 2012). The information presented in Magee (2012) relied on dose-response analyses that were independently performed by ARCADIS in June, 2010 employing EPA’s Benchmark Dose Software (BMDS) (v 2.1.1) software. This modeling resulted in four models that adequately fit the white blood cell response data (Exponential (M2), Exponential (M4), Linear, and Power) and that, when averaged, yielded a BMDL of 11.64 mg/kg-d. The ARCADIS approach differed modestly from the approach taken by Thompson et al. (2013) and Gradient (2014), but produced a comparable BMDL estimate. The ARCADIS BMDL analyses used to develop the position presented in Magee (2012) are alternative analyses to those described by Gradient (2014) and Thompson et al. (2013). Taken together, the results indicate that comparable BMDL estimates have been reached by different groups of researchers, using different versions of EPA’s modeling software and assumptions.

**COMMENT 2**: In reference to Magee (2012), Gradient states the following on page 31:

*“We note that there is a discrepancy in the discussion of model averaging by Magee (2012). On page 7, it states:*

*the white blood cell data using historical controls provided BMDLs ranging from 5.54 to 16.12 mg/kg-day, and all* ***five models [emphasis added [by Gradient]]*** *(exponential M2, exponential M4, linear, power and polynomial) gave identical homogeneity variance p-values, goodness of fit p-values, and AIC values. Further, even though* ***all four models [emphasis added [by Gradient]]*** *met the scaled residual criterion of absolute value <2, the scaled residuals for the linear, power, and polynomial models showed a slightly better fit to the data than the two exponential models (M2 and M4)…”*

**RESPONSE 2**: We agree that there is a discrepancy between the two bolded sections of text. There is a typographical error in Magee (2012) when reporting the results of ATSDR (2011). Both sections of bolded text identified by Gradient (2014) should state “five models” when referring to the ATSDR (2011) results. In Magee (2012), ARCADIS confirmed that the ATSDR (2011) identified five models that adequately fit the HLS (2011) data: Exponential (M2 and M4), Linear, Power, and Polynomial. Results associated with the polynomial and power models were not presented in ATSDR’s Tables B-4, B-5, B-5, and B-7, because the results were identical to those obtained using the linear model.

**COMMENT 3***:* In reference to Magee (2012), Gradient states the following on page 31:

*“ARCADIS verified the white blood cell benchmark dose modeling of ToxStrategies 2011 [sic], specifically, the female rat BMDL values for the white blood cell decrements using the historical control variance are 8.78, 5.55, 16.12 and 16.12 mg/kg-day, for each of 4 BMD model types, with an average BMDL of 11.64 mg/kg-day. All models are acceptable fits to the experimental data, and the AIC values for the four models are identical. Thus, the USEPA's default averaging approach is appropriate for setting a Point of Departure. (Magee, 2012).*

*It appears from this discussion that there may have been an error in the average provided for the WBC counts. As summarized in Table 3.13, there are indeed five models that provided adequate fits to the log-transformed WBC data (exponential M2, exponential M4, linear, power and polynomial). Thus, the average of the five BMDLs (16.12, 16.12, 16.12, 5.54, and 8.78 mg/kg-day) would be 12.54 mg/kg-day instead of 11.64, as cited above.*”

**RESPONSE 3**: It is correct that Magee (2012) determined that the polynomial model did not adequately fit the HLS study’s white blood cell count data (2001). As a result, the average BMDL was calculated using output from the four models that adequately fit the data (Exponential (M2), Exponential (M4), Linear, Power). This resulted in an average BMDL of 11.64 mg/kg-day. The source of the discrepancy between Magee (2012) and Gradient (2014) is related to the way that restrictions were applied to polynomial coefficients (*β*) during parameterization of the BMD model.

The BMD software used by Magee (2012) (EPA BMDS v 2.1.1) and Gradient (2014) (EPA BMDS v 2.5) allow users to choose whether or not to apply restrictions to polynomial model *β*’s, specifically restrictions to either positive or negative values. However, the software version used by Magee (2012) (BMDS (v 2.1.1)) requires users to manually select whether or not to restrict the *β*’s and, if restricted, whether to restrict the values to positive values or negative values. Magee (2012) did not apply restrictions to *β’s* during modeling. When the polynomial model was then evaluated to determine if it fit the data, Magee (2012) found that the polynomial model did not provide an adequate global goodness-of-fit (p-value = 0.078). In contrast, Gradient (2014) employed BMDS (v 2.5) in combination with the BMD Wizard (v 1.9). This version of the BMD Wizard restricts *β*’s to non-positive values by default. Gradient (2014) did not indicate whether it adjusted any of the default settings of the BMD Wizard, so ARCADIS assumes that Gradient (2014) used the default settings. Under the default modeling conditions, Gradient (2014) found that polynomial models did adequately fit the white blood cell count data.

EPA guidance (2000) does not provide any recommendations for applying restrictions to polynomial model *β’*s. EPA (2012) recommends usually restricting polynomial *β*’s to ≤ 0 for decreasing response data “to ensure monotonic curves.” When Magee (2012) fit polynomial models parameterized with non-restricted *β*’s to the white blood cell count data, he found that the model produced a monotonic dose-response curve. Thus, Magee (2012) did not find any evidence to require restricting *β*’s to non-positive values.

**COMMENT 4**: In reference to Magee (2012), Gradient states on Page 36, Table 4.2 that:

“*ARCADIS relied upon BMDL estimates from Thompson et al. (2013) and averaged the BMDLs from four viable models (using historical control data). (Note this is equivalent to Approach 3 from Table 4.1, however the average was calculated incorrectly and should equal 12.54 mg/kg-day)*.”

**RESPONSE 4**: As noted above, ARCADIS independently calculated BMDLs using the biological effects data reported in the Huntingdon Life Sciences (2001) study in combination with EPA BMD guidance (1995, 2000, 2012). The information presented in Magee (2012) relied on dose-response analyses that were performed in June, 2010 using EPA’s BMDS (v 2.1.1) software. It is correct that Magee (2012) determined that the polynomial model did not fit the data, and as a result the average BMDL was calculated based on the output from the four models that did adequately fit the data (Exponential (M2), Exponential (M4), Linear, and Power). This approach resulted in an average BMDL of 11.64 mg/kg-day. However, information in Tables 3.4 and 4.2 of Gradient’s report (2014) indicates that polynomial models, in addition to the aforementioned models, also adequately fit the female rat white blood cell count data (HLS, 2001). The source of the discrepancy is related to the way that restrictions were applied to polynomial coefficients (*β*) during parameterization of the dose-response model and is addressed in ARCADIS’ response to comment 3. ARCADIS did not average the data incorrectly, but rather properly calculated an average BMDL using EPA guidance with EPA software available at the time. Based on this modeling with version 2.1.1 of EPA’s BMD software, ARCADIS’ results differ modestly from the approach taken by Gradient (2014) and Thompson et al. (2013).

**REFERENCES**

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