Petitioner AMVAC Exhibit 33

EPA OALJ Docket No. FIFRA-HQ-2022-0002

Comments on DCPA CTA Protocol

On Thursday, July 8, 2021, the Agency discussed the study protocol for the definitive Pre- and Post-Natal Developmental Comparative Thyroid Assay (CTA) in Sprague Dawley Rats by Oral (Gavage) Administration along with the submitted range-finding studies and method validation studies. Based on the results from the range-finding studies, the registrant proposed dose levels including 0.1, 1, 10, and 100 mg/kg/day for the definitive study and the thyroid hormone levels would be measured two hours following administration of DCPA.

While reviewing the relevant data for dose selection, the Agency recommends 0.05, 0.1, 1, and 10 mg/kg/day as the selected dose levels for the definitive study to identify a clear NOAEL and LOAEL for the study. The Agency notes abnormal changes in thyroid hormone levels at 0.1 mg/kg/day and recommends that this dose level be included as a dose level. At 10 mg/kg/day, serum thyroxine (T4) levels were significantly decreased in male and female fetuses (↓74% and ↓77% ($p<0.01$), respectively) and the results from the range-finding studies suggest that the fetus is the most sensitive life-stage to DCPA compared to the offspring and adults. Therefore, the Agency recommends 10 mg/kg/day as the high dose for the definitive CTA study.

The Agency recommends that the thyroid hormone levels for all lifestages be measured three hours following the administration of DCPA instead of two hours as suggested by the registrant. Newly submitted milk transfer data demonstrates that three hours post-dosing provides sufficient time for the chemical to pass through the milk. In addition, the metabolism data suggest that after three hours, the peak level of the radiolabeled compound is present in the blood at a low dose (1 mg/kg). Given that detectable levels of DCPA are present in the milk at the suggested lower doses and the levels of DCPA in the milk increase with dose, the Agency agrees the direct dosing of pups is not necessary.

The Agency recommends that the registrant consider using LC-MS/MS as the method to measure all thyroid hormone levels (T3, T4, and TSH) to reduce the level of variability that was identified with measuring TSH. The Agency recommends that the relative error of at least 67% of the QC samples should be within 20% of the nominal concentration, including at least 75% at each concentration levels.

The Agency noted that the definitive study is scheduled to occur at Covance while the previous studies occurred at Envigo. The Agency recommends that the registrant clarify that the facility where the method validations, and range-finding studies occurred is the same laboratory where the definitive study will occur.

A final memo that documents the Agency's recommendations will be forthcoming.