Petitioner AMVAC Exhibit 25

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

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 19-MARCH-2020

SUBJECT: Protocol review for an updated range-finding comparative thyroid assay for dimethyl tetrachloroterephthalate (DCPA)

PC Code: 078701
Decision No. : 559712
Petition No. : NA
Risk Assessment Type: NA
T**XR No. :** 0057999
MRID No. : NA

DP Barcode: D456384
Registration No. : NA
Regulatory Action: Study Plan Review
Case No. : NA
CAS No. : 1861-32-1
40 CFR: 180.185

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I. ACTION REQUESTED: The Agency has been asked to review an updated protocol for a dose range-finding comparative thyroid assay (CTA) for dimethyl tetrachloroterephthalate (DCPA). The study plan (study # PM86YP) submitted by the registrant (AMVAC) includes evaluations of milk transfer of DCPA and thyroid hormone levels in dams and pups (including a PTU positive control group) in Sprague-Dawley rats through oral administration of DCPA. The proposed study seeks to quantify the amount of DCPA passed via milk to offspring in the range-finding study to better determine the proper dosing administration and dose levels for a definitive developmental study of DCPA.

II. CONCLUSIONS: The study plan was reviewed by the Agency and the protocol is considered adequate for a range-finding study with the following recommendations noted (see Discussion section, below). The Agency strongly recommends submitting the results of the range-finding study with a protocol of a definitive study for discussion with the Agency prior to commencing the definitive CTA.

III. BACKGROUND INFORMATION: The Agency previously reviewed a study plan (TXR 0057935, D420813, O. Triplett, 09/17/2019) for conduct of a CTA for DCPA submitted by AMVAC. The proposed study plan consisted of two phases. The first (labeled Phase I) was a range-finding assay that was to be used to help determine final doses for a more definitive study termed Phase II. Phase II was to be the definitive CTA. The Agency recommended a tiered approach to conducting the proposed studies with Phase I conducted prior to initiating Phase II in order to determine the proper dosing administration for pups and appropriate dose levels for the study. The Agency also indicated that a detailed study protocol be submitted for the Agency to review before commencing the proposed studies that includes only the Phase I portion with the DCPA measurements in milk and, if possible, some thyroid measurements in serum. Based on this previous response, AMVAC has provided a detailed protocol for Phase I to evaluate milk transfer of DCPA and thyroid hormone levels in dams and pups. The proposed dose range of DCPA for this study are 0.01, 0.1, 1.0 and 10 mg/kg/day.

IV. DISCUSSION:

6.2.1 Environmental Control

Please clarify if air supply has at least 10 air changes per hour in the final report.

6.2.2 Animal Accommodation

It is noted that the laboratory (Covance) has a stated policy permitting social interaction through multiple housing of rats whenever possible. The Agency recommends that animals be housed individually.

8.2 Maternal and offspring milk sampling and analysis for concentrations of DCPA

Ensure that the LC-MS/MS methods are appropriately validated before beginning the study and any validation methodology and data be included in the final report. Validated study results need to be reviewed by the Agency for the LC-MS/MS methods before the start of the definitive CTA study. Calibration curves should be provided and data on the sensitivity of the assay (Lower Limit of Quantification or LLOQ) for LC-MS/MS be submitted in the final report.

8.3 Thyroid hormone analyses

Due to the circadian rhythm of thyroid hormones, the Agency recommends ensuring that sample collection occurs at approximately the same time of day and be randomized across dosage groups, preferably in the morning hours at which time basal values should be present.

Animals should have a pre-sampling sequestration in a quiet space separated from the sacrifice room and allowed to habituate to holding room prior to sacrifice to reduce stress-induced hormonal fluctuations.

Animals should be sacrificed using a single method, independently of their life stage. Decapitation without use of anesthesia is the preferred method of sacrifice.

The proposed methods appear to be adequate for the intended purpose of detecting thyroxine (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH). The method details used for thyroid hormone detection should be provided. For all assays, the registrant should provide calibration curves, the sensitivity of the assay (Lower Limit of Quantification or LLOQ), and the assay should be able to detect thyroid hormone (T4) at nanogram range).

For TSH, an immunoassay kit is proposed for measurements by the registrant. The sensitivity limit of the assay should be tested and determined within the lab with the standards provided in the kit in addition to serum samples from the positive control animals or serum with a known hormone profile using internal quality control practices. The registrant should provide calibration curves and submit data on the sensitivity of the assay (Lower Limit of Quantification or LLOQ) and include the inter- and intra- assay variability. The Agency recommends that samples be run in duplicate.

If there are an inadequate number of fetuses in a litter to obtain sufficient blood for the hormonal measures, the measurements of T4 and TSH (if feasible) would be a priority, with less emphasis placed on T3 measures. If necessary, PND 4 pups of both sexes may be pooled to achieve sufficient blood sample. Fetal samples should be pooled from the same dam. The registrant has provided historical vehicle control data validation indicating that TSH levels in all animals tested were above the validated LLOQ of 123 pg./mL.

General Comments:

The Agency notes that individual animal data must be included in the final report for all groups.

The historical control data provided for validation should also be provided with the final report.

It is recommended that the registrant submit results of the range-finding study for discussion with the Agency before commencing the definitive CTA.