Petitioner AMVAC Exhibit 19

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: 17-SEP-2019

SUBJECT: Study Plan review for a range-finding and comparative thyroid assay for dimethyl tetrachloroterephthalate (DCPA)

PC Code: 078701
Decision No.: 492006
Petition No.: NA
Risk Assessment Type: NA
T**XR No.:** 0057935
MRID No.: NA

DP Barcode: D420813
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. CONCLUSIONS: A study plan (JW36WK) for a dose range finding study and pre-and post-natal developmental thyroid study involving Dacthal (dimethyl tetrachloroterephthalate or DCPA), has been submitted by the registrant. These plans include efforts to quantify the amount of DCPA passed via milk to offspring and confined in plasma prior to initiation of an assessment of possible effects of DCPA on thyroid function. The study plan review was conducted by the Agency and the results are discussed below.

II. ACTION REQUESTED: Please review the proposed study plan and accompanying documents for the DCPA range-finding and comparative thyroid assay (CTA). The submitted study plan was an overview of the proposed approach to conduct the indicated studies and not a detailed study protocol.

III. BACKGROUND INFORMATION:

The submitted study plan is a modification based upon the Agency's previous review of a previous protocol for a range-finding pre- and post-natal developmental thyroid study (TXR 0057666, D444017, L. Taylor, 11/16/2017; see Attachment A). The selected dosages of DCPA for the proposed range finding study are 0.01, 0.1, 1 and 10 mg/kg/day as indicated in the study plan. The proposed study plan consists of two parts; Phase I, an apparent range finding study that incorporates a determination of the DCPA concentrations contained in milk and serum in both pups and dams. Phase II consists of a developmental thyroid evaluation and contains a PTU positive control.

The proposed study plan submitted is acceptable with the following recommendations noted below

IV. DISCUSSION:

The Agency would suggest referring to the "Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals" to ensure adherence to proper procedures to produce usable data from these studies. This guidance can be found at the following address: https://www.epa.gov/pesticide-registration/guidance-thyroid-assays-pregnant-animals-fetuses-and-postnatal-animals

The Agency also recommends a tiered approach to conducting the studies proposed in the submitted study plan. Phase I, the proposed range finding study, should be conducted before initiating Phase II, the proposed pre-and post-natal developmental thyroid studies. The Agency would like to review a detailed study protocol that includes only the Phase I portion with the DCPA measurements in milk and if possible, some thyroid hormone measurements in serum. This information will help determine:

(a) if DCPA/metabolites can be found in milk, and

(b) if thyroid hormones can be detected in dams and pups using the proposed immunoassay.

The study design and protocol for Phase II will be dependent upon the ability to detect DCPA (and major metabolites, if appropriate) in milk, and serum. The milk measurements in the range-finding study should guide the study design for the definitive study, i.e. some of the treatment

groups proposed currently may or may not be necessary if DCPA/metabolites are found or not found in milk.

The proposed methods using HPLC MS/MS appear to be adequate for the intended purpose of detecting thyroxine (T4), triiodothyronine (T3), and DCPA in milk and plasma. For the HPLC-MS/MS the Agency recommends including internal standards and calibration curves in the final report.

The proposed immunoassay, while sensitive to about 16 pg/ml, still needs to be further refined. The Agency would highly recommend that Envigo laboratory provide method validation data for the thyroid hormone assays to demonstrate similar or very close results as those indicated by the manufacturer for its immunoassay method. The Agency would recommend the registrant resubmit the calibration curve data and improved % CV values with the completed protocol for Phase I Agency review before commencing with the proposed studies.

The Agency would again like to stress the need to submit a detailed study protocol based on the Phase I study plan and submit it for Agency review before commencing any work. Additionally, it is recommended that the registrant needs to complete Phase I and submit results to the Agency before the final Agency review of the definitive comparative thyroid assay study (Phase II) protocol can be evaluated. The Phase I range-finding study should be used to optimize doses and sampling times and to determine whether direct dosing of pups will be necessary for the definitive (Phase II) range-finding study.

Attachment A

TXR 0057666 review, 2017

UNITED STATES ENVIRONMENTAL PROTECTIONAGENCY
WASHINGTON, D.C. 20460
Office of Chemical Safety & Pollution Prevention

MEMORANDUM

Date: November 16, 2017

SUBJECT: **DCPA:** HED Review of the Comparative Thyroid Assay Range-Finding Study and Thyroid Hormone Methods Data.

PC Code: 078701
Decision No.: NA
Petition No.: NA
Risk Assessment Type: NA
T**XR No.:** 0057666
MRID No.: NA

DP Barcode: D444017
Registration No.: NA
Regulatory Action:
Case No.: NA
CAS No.: 1861-32-1
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I. CONCLUSIONS: A new range-finding pre- and post-natal developmental thyroid study using the HPLC-MS-MS method for T4, TSH, and T3 in serum is required. The study should incorporate all aspects (data the current Phases II and III were to provide) such that the results will directly determine the dose levels, time points, and whether pups will need to be dosed directly in the definitive comparative thyroid study.

II. ACTION REQUESTED: Please review the revised protocol for the DCPA comparative thyroid test, which was modified after HED's previous assessments of the original protocol.

III. BACKGROUND: Although this action is listed as a protocol review, the primary request was for an assessment of the dose levels and time point to be used in the next phases of the range-finding study. This is the third HED review of the protocol for the comparative thyroid assay (CTA) for DCPA (TXR# 0056835, dated 11/19/2013 and TXR# 0054026, dated 4/16/2015 for previous reviews). For the current action, the registrant submitted (*via* email) the results of a dose range-finding (DRF) pre- and post-natal developmental thyroid study (Envigo Study BDG0204) and requested comment on their dose selection (0. 0.1, 1, 10, or 100 mg/kg/day) and time-point (2 hours) for thyroid assessment for use in Phase II and Phase III of the DRF study. The results submitted in the current action are those from a repeat of the Phase I of the DRF study (Phase 1a) since problems with the thyroid assay methodology were encountered in the first Phase 1 study.

Subsequent to the request for approval of their dose levels and time point, Amvac submitted (1) the positive control (PTU) pre- and postnatal developmental thyroid study report (MRID 50357301), which was listed in the 2015 protocol review as required; (2) a validation report (HLS0980) for the immunoassay method used for TSH assessment in Phase 1a and the PTU studies; and (3) additional information on thyroid hormone assay methodology [validation for the GC-MS/MS method (FF58YR)] used in Phase 1a for T4 and T3 assessment and scheduled for use in the subsequent phases of the DRF study.

The validation data for TSH for the HPLC MS/MS method has not been submitted to date.

IV. RESULTS/DISCUSSION: The protocol revision, thyroid hormone assay methodology, Phase 1a thyroid hormone results, and dose levels and time point selection were discussed by HED's Toxicology Science Advisory Council (ToxSAC) on October 19, 2017, *four years after the original protocol was reviewed and 2.5 years after the original Data Call-In (DCI) due date for completion of the CTA (January 2015).* The following concerns were identified with respect to the DCPA developmental thyroid studies (BDG0204).

1) ToxSAC concurs with the HPLC-MS-MS approach for thyroid hormone assessment (all three hormones in serum) and, if the TSH validation data are adequate, it will then be necessary to perform a new range-finding study using this HPLC-MS-MS method and the dose levels used previously. This new range finding study should provide thyroid hormone (T4, TSH, T3 in serum and milk) data and incorporate all aspects such that the results will directly determine the dose levels, time points, and whether pups will need to be dosed directly in the definitive study. Measurement of the thyroid hormones should be at the same time of day, preferably in the morning. Thyroid hormone data are needed for the GD 20 dams, fetuses, and LD 4, LD 14, LD 21 pups. Dosing of the dams should be continued until PND 14 (until the pups begin to eat the feed); gavage dosing of the pups should be from PND 7 to PND 20/21 (current Phase III).

2) To address whether DCPA gets into the milk, the milk sampling method should be clarified. Frequent milk samples should be taken (Day 1, 7, 14, and 21). Additionally, it would be useful to know how long DCPA stays in the milk after dosing has stopped.

3) The dose levels to be used in the definitive study (Envigo Study # BDG0202) are contingent on the results of the new RF study, which will need to be re-assessed by ToxSAC before the definitive study is performed.

4) Validation data for TSH for HPLC MS/MS method are required, which the registrant has

stated will be submitted in November 2017. These data will need to be assessed prior to moving forward with the new RF study (described above).

5) SOPs and the final study protocol for the definitive study need to be submitted to the Agency for review prior to initiation of the definitive study.

6) The PTU study report does not provide any useful data in support of the testing facility's ability to monitor thyroid hormones since the immunoassay method (HLS0980) used, which assessed all three hormones in plasma, is not the method scheduled for use in the definitive study.

7) For the current range-finding study (BDG0204) protocol Phase II, the dams are to be dosed from gestation day (GD) 6 through lactation day (LD) 20/21, but there is no mention of whether the levels of DCPA in the milk will be analyzed in Phase II. Samples of milk should be measured in Phase II (LD 1, 7, 14, and 21). There is no information as to when thyroid hormones are being monitored in this phase in dams and pups. In Phase III, why are the dams dosed only through LD 7 and not through LD 14? Are the levels of DCPA in milk being measured in Phase III? How are the pups being dosed (gavage or through the feed)? The pups would still be nursing on LD 7 and beyond, so double dosing could occur. When are thyroid hormones being assessed in the dams and pups in Phase III? Phase III appears to be more appropriate for the definitive study if it is determined (in Phase II) that DCPA does not get into the milk, in which case the dams could continue to be dosed to Day 20/21. As discussed above, a new range-finding study is required, which should incorporate all of these phases into one study.

V. CONCLUSION: A new range-finding pre- and post-natal developmental thyroid study using the HPLC-MS-MS method for T4, TSH, and T3 (in serum) is required. The study should incorporate all aspects (whatever data the current Phases II and III were to provide) such that the results will directly determine the dose levels, time points, and whether pups will need to be dosed directly in the definitive CTA study.